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Oral switch versus standard antibiotic therapy in left-sided endocarditis due to susceptible staphylococci, streptococci or enterococci (RODEO): a protocol for two open-label randomised controlled trials

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ABSTRACT

Introduction

Left-sided infective endocarditis (IE) is a serious infection with a heavy burden for patients and healthcare system. Oral switch after initial intravenous antibiotic therapy may reduce costs and improve patients' discomfort without increasing unfavourable outcomes. We describe the methodology of two simultaneously conducted open-label randomised trials aiming to assess non-inferiority of oral switch as compared to entirely intravenous antibiotic therapy for the treatment of left-sided IE.

Methods and analysis

Two multicentre open-label prospective randomised trials assessing non inferiority of oral switch during antibiotic treatment as compared to entirely intravenous therapy in patients with left-sided IE are ongoing. One trial is dedicated to left-sided IE caused by multi-susceptible staphylococci and the other is dedicated to left-sided IE caused by susceptible streptococci or enterococci. It is planned to randomise 324 patients in each trial after an initial course of at least 10 days of intravenous antibiotic therapy either to continue intravenous antibiotic therapy or to switch to oral antibiotic therapy. The primary outcome is treatment failure within 3 months after the end of antibiotic treatment, a composite outcome defined by all-cause death and/or symptomatic embolic events and/or unplanned valvular surgery and/or microbiological relapse (with the primary pathogen). Secondary outcomes include patient quality of life, echocardiographic outcome, costs and efficiency associated with IE care. Statistical analysis will be performed with a non-inferiority margin of 10% and a one-sided 2.5% type I error.

Ethics and dissemination:

Written informed consent will be obtained from all participants. This study was approved by Tours Research ethics committee (CPP TOURS - Region Centre - Ouest 1, 2015-R26,

23/02/2016). Study findings will be published in peer-reviewed journals and disseminated through presentation at relevant national and international conferences.

Registration details:

The trials are registered with the European Clinical Trials Database (EudraCT Number: 2015-002371-16) and on clinicaltrials.gov (NCT02701608 and NCT02701595).

Keywords:

Infective endocarditis, oral administration, randomized controlled trial, anti-bacterial agents, adult

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ARTICLE SUMMARY

Strengths and limitations of these studies

- RODEO trials are multicentre randomised controlled trials appropriately designed and powered to assess non-inferiority of oral switch of antibiotic therapy as compared to entirely intravenous antibiotic therapy in patients with left-sided infective endocarditis
- An economic evaluation, including a cost analysis, a cost-utility analysis and a budget impact analysis, will be conducted alongside the trials. Results will be provided separately since each type of left-sided IE management will be compared to the real-life situation.
- In these trials, few regimens are proposed for oral switch, in line with local epidemiology with a relative paucity of resistant bacteria, thus allowing a better homogeneity in the analysis. It will therefore be necessary to take precautions when extrapolating the results.
- Limitation due to the open-label design of those randomised trials will be limited by the use of a blinded committee to adjudicate the primary outcome.

Introduction

Infective endocarditis (IE) is a serious infectious disease with a heavy burden for patients and healthcare system (1). In France, median length of hospital stay for patients with IE is 43 days (2) partly linked to the prolonged intravenous (IV) antibiotic therapy recommended by international guidelines (between 4 and 6 weeks in most situations) (3). Current guidelines for IE management are mostly based on expert opinion, *in vitro* studies, animal experiments, or clinical studies performed before the 90's, as very few randomised studies have been conducted (4,5). The only exception to the golden rule of 'IV treatment for all IE' is right-sided IE due to meticillin-susceptible *Staphylococcus aureus* (MSSA), in which the efficacy of an oral combination of ciprofloxacin and rifampicin has been validated in one randomised trial which only included 44 patients (6). Most experts acknowledge that the pharmacodynamic and pharmacokinetic characteristics of antibiotics such as amoxicillin, fluoroquinolones and rifampicin allow a high level of efficacy in the treatment of IE when orally administrated after an initial phase with adequate IV antibiotic therapy (7–12) . A recent systematic review of oral therapy for the treatment of right- or left-sided IE found only one observational study reporting 80% cure rate with oral amoxicillin in 15 cases of streptococcal left-sided IE (13). Two recent studies regarding the management of IE in France showed that a switch from IV to oral antibiotics is feasible when patients with left-sided *Staphylococcus* or *Streptococcus* IE are stable after an initial course of IV antibiotic treatment, with or without valvular surgery (14,15). These practices have not been associated with unfavourable outcome, while significantly reducing the duration and cost of hospitalization, the risk of nosocomial infection, and patients' discomfort. A first randomised trial recently found non-inferiority of partial oral treatment as compared to continued intravenous antibiotic treatment in IE due to Gram-positive cocci whatever its species (16). Other well-designed randomised controlled trials are however needed to confirm the clinical

non-inferiority of this strategy in IE due to most common bacteria (multisusceptible staphylococci, susceptible streptococci or enterococci), specifying for each group of species. Addressing these bacteria in two simultaneously performed trials would ensure an optimal recruitment, reduce cost of research, and argue for/against oral switch in the majority of IE patients. The RODEO project corresponds to two pragmatic open-label randomised trials assessing non inferiority of oral switch during antibiotic treatment as compared to entirely intravenous standard-therapy in patients with left-sided IE. One trial is dedicated to left-sided IE caused by multi-susceptible *Staphylococcus* and the other dedicated to left-sided IE caused by multi-susceptible *Streptococcus* including *Enterococcus*.

Methods and analysis

Study hypothesis

We hypothesise that oral switch for antibiotic therapy is non-inferior to entirely IV antibiotic therapy in the treatment of left-sided IE as assessed by the proportion of patients with treatment failure within 3 months after the end of antibiotic treatment.

Study design

RODEO project comprises two simultaneously performed nationwide, multi-centre, open-label non inferiority randomised controlled trials comparing oral switch with entirely intravenous antibiotic therapy in patients with left-sided IE and an initial course of at least 10 days of effective intravenous antibiotic therapy. One trial is dedicated to left-sided IE caused by multi-susceptible *Staphylococcus* and the other dedicated to left-sided IE caused by multi-susceptible *Streptococcus* including *Enterococcus*. Both trials are based on the same protocol provided below, they are considered as distinct trials because sample size were calculated, so that each trial will be adequately powered.

Setting

Trials are ongoing at the time of publication in 28 university hospitals, 14 non university hospitals, 3 private hospitals, and 1 military hospital, all in France. The planned duration of the project is 67 months: 60 months for recruitment, and 7 months for maximal follow-up. The first patient was enrolled on February 29, 2016. End of recruitment is planned on February 28, 2021.

Participants

Eligibility criteria

Patients will be considered for inclusion in a trial if they have a left-sided IE and are in a stable condition after an initial course of at least 10 days of intravenous antibiotic therapy. Full eligibility criteria for both trials are listed in Table 1. Most inclusion or non-inclusion criteria are common to both trials, apart from microbiological diagnosis.

Study recruitment

To better coordinate inclusions, only one department is open in each recruiting centre and all but one are in the Infectious Diseases Unit. Potential participants are identified at the time they are hospitalized and receive IV antibiotic therapy for left-sided IE in one of the participating centres. Patients who meet selection criteria receive a brief study presentation and full participant information sheet by a clinician. After selection criteria confirmation and answering to patient questions about the trial, written informed consent is obtained. Baseline data are collected following consent.

Randomisation

Randomisation takes place between Day 10 and Day 28 after initiation of the IV antibiotic therapy (and at least 10 days of IV conventional antibiotic treatment after valvular surgery), once the patient fulfils the inclusion criteria without having non-inclusion criteria and at least 15 days of remaining antibiotic therapy. In each trial, participants are randomly assigned in a

1:1 ratio to experimental group (switch to oral antibiotic treatment) or standard treatment (continuation of IV antibiotic treatment). Randomisation is carried out with stratification on whether or not the patient underwent valvular surgery for the control of the current IE episode. There is one random computer-generated sequence for each trial. Centralised randomisation is performed using a secure web-based randomisation system.

Blinding

Patients and care providers are not blinded for pragmatic reasons (oral versus intravenous treatment).

Nevertheless, this potential bias is counterbalanced by the objectivity of primary outcome assessment (described below) and the presence of an independent blinded Endpoint Committee (EC). The EC is composed of one specialist in infectious diseases, one cardiologist and one microbiologist with expertise in IE management, research methodology and experience with clinical trials. The EC will review each suspected case in order to classify the primary outcome. Adjudication occurs after patients have completed their follow-up. Any disagreements among the EC members will be resolved during conference calls. All decisions made by the Committee are final.

Study interventions

All patients initially receive an IV antibiotic therapy during 10 to 28 days before being randomised if they fulfil the eligibility criteria. The choice of which IV antibiotic agents are used and the expected total duration of antibiotic therapy, from 4 to 6 weeks, should be consistent with the 2015 European Society of Cardiology (ESC) guidelines (3), and is under the responsibility of the physician in charge of the patient. Only patients who still require at least 14 days of treatment for their IE will be randomised.

Experimental group:

Patients switch from initial IV antibiotic therapy to oral antibiotic therapy for the remaining duration of the treatment.

For left-sided IE due to multi-susceptible *Staphylococcus sp.*, patients ≤ 70 kg receive levofloxacin 500 mg once daily in combination with rifampicin 600 mg once daily; patients > 70 kg receive levofloxacin 750 mg once a day in combination with rifampicin 900 mg once a day (11).

For left-sided IE due to multi-susceptible *Streptococcus sp.*, patients ≤ 70 kg receive amoxicillin 1500 mg three times daily and patients > 70 kg receive amoxicillin 2000 mg three times daily.

If an adverse event leads to discontinuation of one antibiotic, the physician in charge of the patient will choose another oral antibiotic agent according to susceptibility testing. The patient will be classified as non-compliant with the strategy if a switch back to IV treatment is needed faced with the impossibility of finishing the remaining oral treatment period.

Control group

Patients keep on IV antibiotic therapy for the remaining duration of treatment.

Study outcomes

Primary outcome

The primary efficacy outcome measure is the occurrence of treatment failure within 3 months after the end of the antibiotic treatment. Treatment failure is a composite outcome and is reached once a patient meets at least one of: 1/ Death from any cause; 2/ Symptomatic embolic events defined as secondary osteo-articular, splenic or brain localization after randomisation. Silent embolic events will not be included; 3/ Unplanned valvular surgery defined as cardiac surgery not planned before randomisation. Surgery due to sterile pericardial effusion or hemorrhage is, however, not included in this end point; 4/

Microbiological relapse (with the primary pathogen) defined as any blood culture positive yielding the same *Staphylococcus sp.* isolate or the same *Streptococcus sp. or Enterococcus sp.* isolate, as the one responsible for the initial episode of endocarditis (i.e. same species, same antibiotic susceptibility profile).

Failures will be confirmed at the end of the follow-up by an independent endpoint adjudication committee, blinded from group allocation.

We also defined a primary safety outcome of all-cause mortality at day 30 after randomisation which will be analysed after recruitment of one third and two thirds of patients within each trial.

Secondary outcomes

The following variables will be compared between allocation groups as secondary outcomes:

1. As advised for composite outcomes, each component of the primary outcome will also be considered independently.
2. Treatment failure within 6 months after the end of the antibiotic treatment.
3. Reinfection defined as the recurrence of positive blood cultures with a different pathogen within 3 and 6 months after the end of antibiotic therapy.
4. Outcome assessed by echocardiography

Ultrasound examinations will measure: left ventricular ejection fraction, apparition, increase or decrease of the following items: vegetation, abscess, perforation, fistula, dehiscence of a prosthetic valve. A control echocardiography will be performed at the end of antibiotic treatment, at 3 months and 6 months after the end of antibiotic treatment.

5. Catheter related adverse events (AE) and healthcare acquired infections as defined:

- Catheter-related AE: infectious (e.g. catheter-related bacteraemia) or non-infectious catheter-related complications (e.g. extravasation, thrombophlebitis)

- Other healthcare-acquired infections, including urinary tract infections, pneumonia, surgical site infection, *Clostridium difficile* infections

6. Quality of life

We will assess patient's quality of life at the end of antibiotic treatment, at 3 months and 6 months after the end of antibiotic treatment, using the EuroQol Five Dimensions (EQ5D3L)

7. Antibiotic modification

All change regarding antibiotic treatment administered will be recorded (drug, dose or duration). We will assess whether there is a need for a return to IV antibiotic in the experimental (oral switch) group.

8. Compliance with oral antibiotic treatment

The assessment of compliance with oral antibiotic treatment will be carried out at each visit during the treatment period though a "patient leaflet" which will permit to note take/omissions of treatment; and through the return of the treatments' boxes to the pharmacy of the investigational site.

9. Economic outcomes

The difference in costs (and length of hospital stays) will be computed from the healthcare system viewpoint between each new strategy of left-sided IE management (depending on the bacteria involved) and the real-life situation. The budget impact of the diffusion of each new strategy will be computed on a three-year timeframe. Incremental cost-utility ratios will be computed to assess the clinical and economic non-inferiority of the two new strategies.

Study procedures

All patients will be followed for a 6-month period following the end of antibiotic treatment. Follow-up is planned as follows: a visit at baseline or Day 1 for randomisation (which is performed between day 10 and day 28 following the start of IV antibiotic therapy), one visit per week during the remaining antibiotic treatment duration, one visit at the end of antibiotic

treatment, and one visit at 14 days, 6 weeks, 3 and 6 months following the end of antibiotic treatment (Figure 1 and 2).

Once a subject will be randomized in the study, every reasonable effort will be make to follow the subject for the entire study period even if there is a deviation from the intervention protocols, an early discontinuation of study treatment or if a participant misses one follow-up visit. If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized. All subjects who discontinue study treatment will be encouraged to complete all remaining scheduled visits and procedures.

Data management

Data is recorded on study-specific electronic case report forms (eCRFs) via an electronic data capture system (eCRF model is available on request to the principal investigator). To maintain participants' anonymity, CRFs are identified only by a patient number and initials. All records that contain patient names or other identifying information will be stored separately from the study records in each centre and can be identified only by the patient number and initials.

Sample size

For sample size calculation, we considered each pathogen separately to ensure that we will have sufficient statistical power to explore non-inferiority of oral switch for staphylococci as well as for streptococci/enterococci. Thus, for each pathogen, *Staphylococcus sp*. and *Streptococcus/Enterococcus sp*., we assumed an expected failure rate of less than 10% (3,17,18), taking into account the fact that we will only enrol patients who have a favourable outcome after the first two weeks of IE treatment), a non-inferiority margin of 10%, a one-sided Type I error of 2.5%, and a power of 80%. The number of subjects required is estimated at 145 evaluable subjects per group, thus a total of 290 randomised patients. It is expected that approximately 10% of patients will not be available for the per-protocol outcome assessment,

leading to a total of 324 patients to be enrolled, to be sufficiently powered for the per-protocol analysis. The total required sample size is thus 648 patients: 324 patients for the *Staphylococcus sp.* IE (RODEO 1 trial), and 324 further patients with *Streptococcus/Enterococcus sp*. IE (RODEO 2 trial).

Statistical analyses

Statistical analyses will be conducted in both intention to treat (ITT) and per protocol (PP) methodology. The PP population will be defined prior to any statistical analysis during a blind review. Analyses will be conducted using two-sided significance tests at the 5% significance level. A participant flow diagram will be reported. Group characteristics at baseline will be studied with descriptive statistics. No statistical tests will be performed on baseline characteristics. For each trial, the rate of the primary outcome will be estimated within each intervention group. Difference of failure rates between entire parenteral treatment and oral switch for the end of antibiotic treatment will be estimated. We will declare oral switch to be non-inferior to parenteral treatment if the lower bound of the one-sided 97.5% CI is greater than –10%.

This analysis will be performed in both the ITT and PP populations. Subgroup analyses will be performed considering the two strata defined by requirement of valvular surgery before randomisation or not.

Statistical analysis will be first performed separately for each trial i.e. for staphylococci IE and streptococci-enterococci IE.

Concerning secondary objectives, the statistical analysis will be the same as for the primary outcome for the components of the primary outcome. Rates of abnormalities will be compared using chi-square tests for echocardiographic outcomes.

Healthcare-acquired infection rates and catheter related non-infectious adverse event rates will be estimated per group and compared using chi-square tests or Fisher exact tests.

Change in health-related quality of life will be analysed considering a linear mixed-effects regression model taking into account repeated measures for a given patient.

Descriptive statistics of compliance with oral therapy will be provided in the experimental group. Analysis will be performed in SAS 9.4 (SAS institute, Cary NC) and R 3.3 (19) softwares (or latest versions).

Economic evaluation

From the data of three recruiting centres, cost analysis will evaluate, from the healthcare system viewpoint, which strategy between the oral switch (after an IV period of induction) or the IV antibiotic treatment (reference strategy) is less costly.

On this basis, the budget impact on the healthcare system of the diffusion of the oral switch strategy will be computed using a budget impact analysis on a three-years' timeframe.

Direct medical costs will be assessed from the healthcare system perspective in both groups and during the whole induction and follow-up period i.e. 6 months after the end of treatment. For each patient, we will collect the healthcare resources used both in the hospital setting and primary care services. This covers the initial hospital stay, subsequent hospital stays due to complications/infections, rehabilitation stay, and antibiotics delivered in primary care. Data will be collected from the local hospital discharge databases of three centres (for hospitalizations) and from the CRF of all patients (rehabilitation care and antibiotics).

Using data from all recruiting centres, a cost-utility analysis will be performed to compute an incremental cost-utility ratio "cost per QALY gained". QALY will be computed from the survival data and utility scores obtained from the responses to the questionnaire EQ5D-3L.

Data monitoring

Clinical research associates will ensure that patient inclusion, data collection, registry and rapport are in accordance with the standard operating procedures of the sponsor and the French Good Clinical Practices. They will verify during the quality control visits (at least

once a year per centre), in collaboration with investigators: the presence of written consent, compliance with the research protocol, the quality of pre-specified data collected in the case report form and its consistency with the 'source' documents and the management of treatments used.

Moreover, a Data Safety Monitoring Committee (DSMC) comprising two independent clinicians and one independent statistician meets approximately every 6 months to discuss any issues related to patient safety. All serious adverse events will be reviewed by the DSMC as well as interim analysis of the primary safety outcome. Interim analyses of all-cause mortality at 30 days following randomisation will be performed after recruitment of one third and two thirds of patients within each trial. Early stopping rule will be to stop the trial for safety concerns if a P value <0.01 is observed. The role and responsibilities of the DSMC are set out in a written charter. The DSMC provides written recommendations to the trial steering committee following each meeting.

Ethics and dissemination

This protocol was approved by local ethics research committee (CPP TOURS - Region Centre - Ouest 1, 2015-R26, 23/02/2016). An agreement from the French national drug safety agency (ANSM) has also been obtained.

In conformity with the Declaration of Helsinki, all participants sign a written informed consent form that describes this study and provides sufficient information for patients to make an informed decision about their participation. Consent is obtained from patients before they undergo any study procedure. Participants may withdraw from the study at any time during the clinical trial without any impact on their care. In that event, data collected prior to participant withdrawal will be used in the trial analysis. Sponsor of the study may audit trial conduct as deemed appropriate. A formal amendment to the local research ethics committee will be required for any amendments to the study protocol which may impact the conduct of

the study, or the potential safety of, or benefits to patients. If needed, an amendment will also be required from the National regulatory Agency for Security of Medicines and healthcare products (ANSM). Any protocol amendments will be communicated to investigators and oversight authority but also to trial participants and registries, if deemed necessary. The 8th amendment was the most recently approved, on December 17, 2018.

Reports will follow international guidelines: CONSORT Statement and Extension of the CONSORT Statement for reporting of non-inferiority and equivalence trials. Research findings will be submitted for publication in peer-reviewed journals regardless of whether or not they are statistically significant. Authors will be individuals who have made key contributions to study design and conduct. Trial findings will also be submitted for presentation at scientific meetings. The study findings will also be presented at relevant national and international conferences.

Patient and public involvement

Patients and public were not involved in the study design, recruitment or conduction of the study. The burden of intervention was assessed by representatives of patient associations participating in the ethical committee. Participants may obtain access to the final results of the study through the local principal investigator.

Discussion

Several recent reviews point out the necessity of high-quality clinical studies in order to improve the level of evidence for the IE management (3,4). The RODEO trials aim to respond to this demand.

Iversen *et al.* in the POET study have recently documented, in a first randomised open-label controlled trial, that a partial oral antibiotic treatment in left-sided IE was non inferior to continued IV treatment and was not associated with unfavourable outcome (16). However,

this study had some limitations which could be addressed in the RODEO study. First, strict inclusion criteria resulted in a large number of exclusions among screened patients (1,554 out of 1,954). We expect that the broader inclusion criteria of the RODEO project will lead to better external validity of the results. Second, unlike the POET study, the oral treatment regimen in our study will be more homogeneous, and closely controlled as the investigational products will be provided and controlled by the trial sponsor. Another limitation in the POET study was the potential bias of merging staphylococci, streptococci, and enterococci for analysis. Indeed, *S. aureus* is regularly isolated as a risk factor for poor outcome in IE (2,17,20), while IE due to streptococci with low minimal inhibitory concentrations (MIC) for amoxicillin could be treated with a short course of IV antibiotic treatment (21).

The RODEO trials will be the biggest multicentre randomised controlled trials to assess non-inferiority of oral switch of antibiotic therapy as compared to entirely intravenous antibiotic therapy in adult patients with left-sided IE due to Gram positive cocci (staphylococci for RODEO 1, streptococci and enterococci for RODEO 2).

If the non-inferiority is confirmed, this strategy could be a way to improve patients' quality of life and reduce IE associated healthcare costs. In order to evaluate this point, a medico-economic evaluation will be conducted alongside the trial.

The pragmatic design of these studies with wide eligibility criteria will permit to evaluate properly the medico-economic analysis, close to the real-life situation.

In the RODEO trials, oral regimens are simplified in the experimental arm, contrarily to the recent POET trial which proposed many different oral combinations (16). Several reasons explain that choice. Firstly, the homogeneity of treatment will be easier to interpret in each of the experimental arm. The combination therapy with rifampicin and quinolones has already been approved in other deep infections due to staphylococci (22,23). For streptococcal IE, oral amoxicillin has been recommended with reassuring results (8,13). Then, this is adapted to

the French epidemiology of infective endocarditis with a relative paucity of resistant bacteria (2,20). Therefore, precaution will have to be taken in the extrapolation of the results, notably for IE due to staphylococci resistant to quinolones and enterococci, as MIC are frequently over 0.5 mg/L (24).

The expected non-inferiority of the experimental arm should help to modify the actual recommendations for IE management. Some retrospective studies had already pointed out the interest of oral switch of antibiotic treatment in IE (6,13,15), and a first randomised assay found the same results (16). The RODEO trials will possibly confirm these conclusions and try to demonstrate a potential medico-economic benefit to this strategy.

Their design will also permit to give robust conclusions for both streptococci and staphylococci IE with appropriate power.

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Author contributions

LB conceived and designed the final trial protocol. AC is responsible for the methodological design of the study and designed the protocol for statistical analysis. SBH is responsible for

the economic evaluation. AL, LB and AC wrote the first draft of the manuscript. LB, PT, JPB, XD, BH and JLM are members of the scientific committee. AL, LB, PT, JPB, XD, BH, JLM and members of the RODEO study group will be investigators and will recruit patients and conduct the trial. All authors read, reviewed and approved the final manuscript.

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Competing interests None.

Ethics approval Tours Research Ethics Committee (CPP TOURS - Region Centre - Ouest 1, 2015-R26, 23/02/2016).

Data sharing statement

There are no plans to grant public access to the full protocol, participant-level data or statistical code. Data from the RODEO trials is stored by the promotor of the trial. Data and the personal identifiers are stored separately and a special permit is required for access to the data. Data can be available on request for academic researchers when it have been analysed and published. Qualified researchers can ask for data sharing by the first author LB after the study finalization.

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Table 1: Eligibility criteria for RODEO 1 and RODEO 2 trials

Inclusion criteria
For both trials
Diagnosis of definite left-sided IE according to Duke criteria (2) on native or prosthetic valve
Age ≥18 year old
Appropriate parenteral antibiotic treatment received for at least 10 days
In case of valvular surgery, appropriate parenteral antibiotic treatment received for at least 10 days after surgery
Planned duration of antibiotics of at least 14 days at the time of randomisation (ensuring to have at least 14 days of oral therapy remaining in the experimental group)
Absence of fever (temperature < 38°C) at each time point during the last 48 hours (at least two measures/day) at the time of randomisation
Negative blood cultures for at least 5 days at the time of randomisation
Informed, written consent obtained from patient
Patient covered by or having the rights to French social security
For RODEO 1: left-sided *Staphylococcus* IE
Left-sided IE due to *Staphylococcus* sp. (*S. aureus* or coagulase negative staphylococci) susceptible to levofloxacin and rifampicin
For RODEO 2: left-sided *Streptococcus* IE
Left-sided IE due to *Streptococcus*/*Enterococcus* sp. susceptible to amoxicillin (MIC ≤ 0.5 mg/l)
Non-inclusion criteria
For both trials
Body mass index <15 kg/m² or > 40 kg/m²
Inability or unwillingness to take oral treatment for any reason (digestive intolerance, significant malabsorption) at the time of randomisation
Absence of an entourage to support and watch for him/her at discharge
Expected difficulties regarding compliance with oral antibiotic treatment or follow-up (e.g. severe cognitive impairment, severe psychiatric disease...)
Valvular surgery planned within the next 6 months
Presence of cardiac devices (pace-maker, implantable cardiac defibrillator) with suspected device-related IE without removal of the device
Breast feeding or pregnancy, or women on childbearing age without effective contraception

Expected duration of follow-up < 7 months at the time of randomisation (e.g. expected life expectancy < 7 months, patient living abroad...)

Past medical history of IE in the last 3 months

Other infection requiring parenteral antibiotic therapy after the randomisation

Inclusion in another interventional clinical trial

For RODEO 1: left-sided *Staphylococcus* IE

Glomerular filtration rate < 50 ml/min/1,73m2 for patients with Staphylococcus sp (*S. aureus* or coagulase negative staphylococci) infection

Contra-indication to oral antibiotics administered in the experimental arm (i.e. fluoroquinolones or rifampicin) - including anticipated non-manageable drug interactions with rifampicin, and allergy or severe intolerance

Taking of an estrogen-progesterone treatment interacting with rifampicin

For RODEO 2: left-sided *Streptococcus* IE

Glomerular filtration rate < 30 ml/min/1.73m2 for patients with Streptococcus/Enterococcus sp. infection

Contra-indication to oral antibiotics administered in the experimental arm (i.e. amoxicillin) - including allergy or severe intolerance

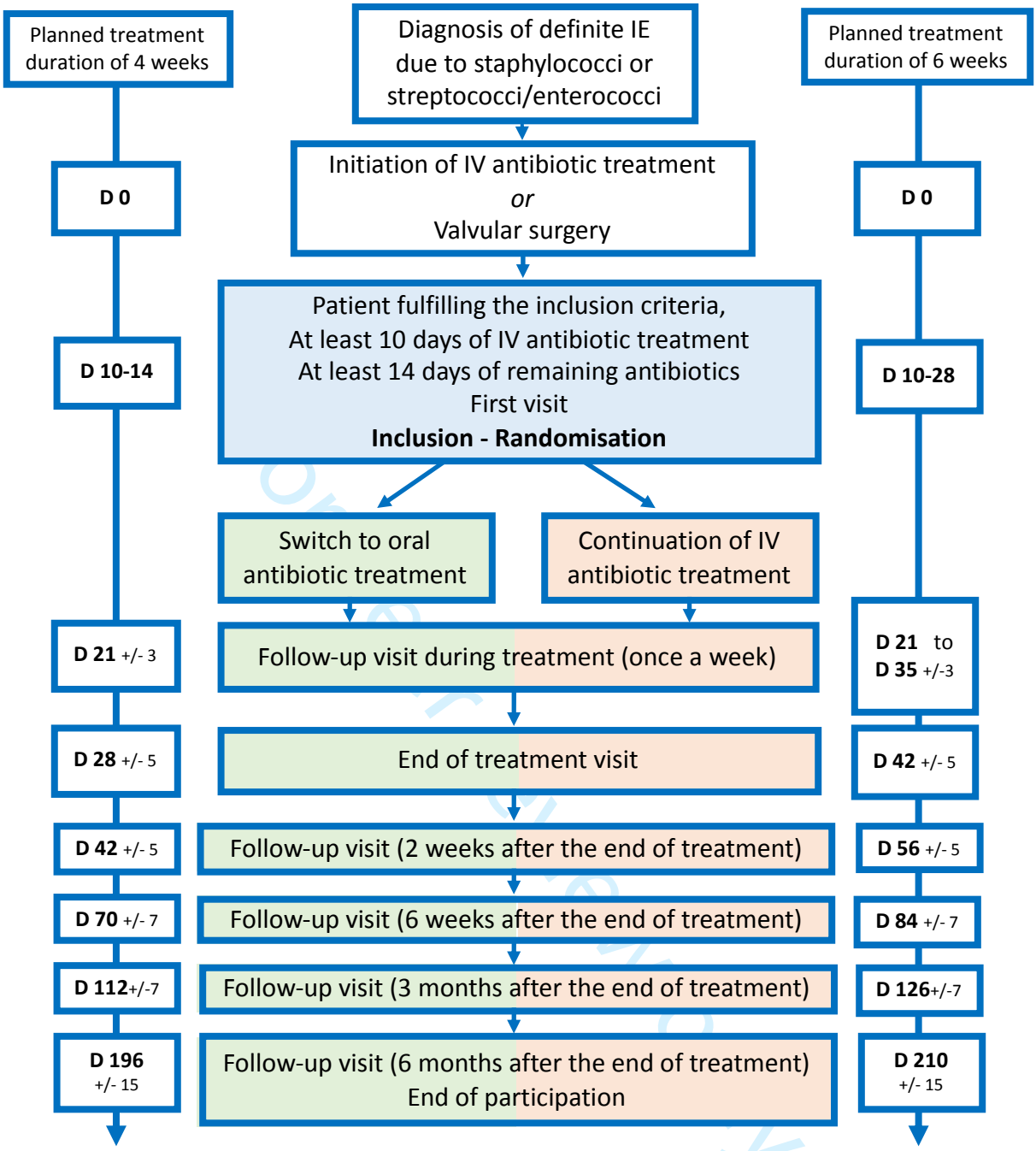

Figure 1: Study design

IE: Infective Endocarditis. IV: intra-veinous

	START OF IV ANTIBIOTIC THERAPY/OR VALVULAR SURGERY (D0)	Visit 1	Per treatment visit (once a week thus from 2 to 4 visits according to the remaining treatment duration at randomisation)	After the end of treatment visit (4 visits for each patient i.e 14 days, 1.5, 3 and 6 months after the end of antibiotic treatment)
Patient information		X		
Criteria for inclusion / non-inclusion		X		
Signature of consent		X		
Randomisation		X		
Socio-demographic characteristics		X		
Clinical information				
History of IE		X		
Clinical examination*		X	X	X
Questionnaire				
Quality of life (EQ5D3L)		X	X (at the end of antibiotic treatment)	X (at 3 months and 6 months after the end of antibiotic treatment)
Compliance with antibiotic treatment			X	
Laboratory tests				
Complete Blood Count		X	X	X
C-reactive protein		X	X	X
Liver function tests Albuminemia, glomerular filtration rate		X	X	
Blood cultures (2 bottles, 10 mL/bottle)		X	X	X
Residual concentration of ATB**			X (at visit 2)	
Blood sample for biological collection		X		
Adverse events and concomitant medications			X	X
Echocardiography		X	X (at the end of antibiotic treatment)	X (at 3 months and 6 months after the end of antibiotic treatment)

Figure 2: Study schedule

*Clinical examination will collect the following information: body temperature, blood pressure, heart murmur (new or modified), any infectious site, list and tolerance of any drug, with a special focus on digestive symptoms, rash, neuropsychiatric complaints.

**Residual concentration of ATB is realized only for patients randomized in "oral therapy" group.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	19
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-4 & 21
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	2

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11, 13, 18, 21
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8-9
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	9
Objectives	#7	Specific objectives or hypotheses	9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11-12 & 26-27
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-12 & 28-29

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	12-13
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	15
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	26-27
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14-15 & 28-29
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15-16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15 & 17-18
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17-18
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18-19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	19
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results	19

		databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	22
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Available on request
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

BMJ Open

Oral switch versus standard intravenous antibiotic therapy in left-sided endocarditis due to susceptible staphylococci, streptococci or enterococci (RODEO): a protocol for two open-label randomised controlled trials

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Oral switch versus standard intravenous antibiotic therapy in left-sided endocarditis due to susceptible staphylococci, streptococci or enterococci (RODEO): a protocol for two open-label randomised controlled trials

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ABSTRACT

Introduction

Left-sided infective endocarditis (IE) is a serious infection with a heavy burden for patients and healthcare system. Oral switch after initial intravenous antibiotic therapy may reduce costs and improve patients' discomfort without increasing unfavourable outcomes. We describe the methodology of two simultaneously conducted open-label randomised trials aiming to assess non-inferiority of oral switch as compared to entirely intravenous antibiotic therapy for the treatment of left-sided IE.

Methods and analysis

Two simultaneous multicentre open-label prospective randomised trials assessing non inferiority of oral switch during antibiotic treatment as compared to entirely intravenous therapy in patients with left-sided IE are ongoing. One trial is dedicated to left-sided IE caused by multi-susceptible staphylococci (RODEO-1) and the other is dedicated to left-sided IE caused by susceptible streptococci or enterococci (RODEO-2). It is planned to randomise 324 patients in each trial after an initial course of at least 10 days of intravenous antibiotic therapy either to continue intravenous antibiotic therapy or to switch to oral antibiotic therapy. The primary outcome is treatment failure within 3 months after the end of antibiotic treatment, a composite outcome defined by all-cause death and/or symptomatic embolic events and/or unplanned valvular surgery and/or microbiological relapse (with the primary pathogen). Secondary outcomes include patient quality of life, echocardiographic outcome, costs and efficiency associated with IE care. Statistical analysis will be performed with a non-inferiority margin of 10% and a one-sided 2.5% type I error.

Ethics and dissemination:

Written informed consent will be obtained from all participants. This study was approved by Tours Research ethics committee (CPP TOURS-Region Centre-Ouest 1, 2015-R26,

23/02/2016). Study findings will be published in peer-reviewed journals and disseminated through presentation at relevant national and international conferences.

Registration details:

The trials are registered with the European Clinical Trials Database (EudraCT Number: 2015-002371-16) and on clinicaltrials.gov (NCT02701608 and NCT02701595).

Keywords:

Infective endocarditis, oral administration, randomized controlled trial, anti-bacterial agents, adult

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ARTICLE SUMMARY

Strengths and limitations of this study

- RODEO 1-2 trials are multicentre randomised controlled trials appropriately designed and powered to assess non-inferiority of oral switch of antibiotic therapy as compared to entirely intravenous antibiotic therapy in patients with left-sided infective endocarditis
- An economic evaluation, including a cost analysis, a cost-utility analysis and a budget impact analysis, will be conducted alongside the trials.
- In these trials, few regimens are proposed for oral switch, in line with local epidemiology with a relative paucity of resistant bacteria, thus allowing a better homogeneity in the analysis.
- Limitation due to the open-label design of those randomised trials will be limited by the use of a blinded committee to adjudicate the primary outcome.

Introduction

Infective endocarditis (IE) is a serious infectious disease with a heavy burden for patients and healthcare system (1). In France, median length of hospital stay for patients with IE is 43 days (2) partly linked to the prolonged intravenous (IV) antibiotic therapy recommended by international guidelines (between 4 and 6 weeks in most situations) (3). Current guidelines for IE management are mostly based on expert opinion, *in vitro* studies, animal experiments, or clinical studies performed before the 90's, as very few randomised studies have been conducted (4,5). The only exception to the golden rule of 'IV treatment for all IE' is right-sided IE due to meticillin-susceptible *Staphylococcus aureus* (MSSA), in which the efficacy of an oral combination of ciprofloxacin and rifampicin has been validated in one randomised trial which only included 44 patients (6). Most experts acknowledge that the pharmacodynamic and pharmacokinetic characteristics of antibiotics such as amoxicillin, fluoroquinolones and rifampicin allow a high level of efficacy in the treatment of severe infections due to *S. aureus*, including IE, when orally administrated after an initial phase with adequate IV antibiotic therapy (7–12). A recent systematic review of oral therapy for the treatment of right- or left-sided IE found only one observational study reporting 80% cure rate with oral amoxicillin in 15 cases of streptococcal left-sided IE (13). Two recent studies regarding the management of IE in France showed that a switch from IV to oral antibiotics is feasible when patients with left-sided *Staphylococcus* or *Streptococcus* IE are stable after an initial course of IV antibiotic treatment, with or without valvular surgery (14,15). These practices have not been associated with unfavourable outcome, while significantly reducing the duration and cost of hospitalization, the risk of nosocomial infection, and patients' discomfort. A first randomised trial recently found non-inferiority of partial oral treatment as compared to continued intravenous antibiotic treatment in IE due to Gram-positive cocci whatever its species (16). Other well-designed randomised controlled trials are however

needed to confirm the clinical non-inferiority of this strategy in IE due to most common bacteria (multisusceptible staphylococci, susceptible streptococci or enterococci), specifying for each group of species. Addressing these bacteria in two simultaneously performed trials would ensure an optimal recruitment, reduce cost of research, and argue for/against oral switch in the majority of IE patients. The RODEO project corresponds to two pragmatic open-label randomised trials assessing non inferiority of oral switch during antibiotic treatment as compared to entirely intravenous standard-therapy in patients with left-sided IE. One trial is dedicated to left-sided IE caused by multi-susceptible *Staphylococcus* and the other dedicated to left-sided IE caused by multi-susceptible *Streptococcus* including *Enterococcus*.

Methods and analysis

Study hypothesis

We hypothesise that oral switch for antibiotic therapy is non-inferior to entirely IV antibiotic therapy in the treatment of left-sided IE as assessed by the proportion of patients with treatment failure within 3 months after the end of antibiotic treatment.

Study design

RODEO project comprises two simultaneously performed nationwide, multi-centre, open-label non inferiority randomised controlled trials comparing oral switch with entirely intravenous antibiotic therapy in patients with left-sided IE and an initial course of at least 10 days of effective intravenous antibiotic therapy. One trial is dedicated to left-sided IE caused by multi-susceptible *Staphylococcus* (RODEO-1 trial) and the other dedicated to left-sided IE caused by multi-susceptible *Streptococcus* including *Enterococcus* (RODEO-2 trial). Both trials are based on the same protocol provided below. Nevertheless, they are considered as two distinct trials, and sample sizes were calculated separately so that each trial has 80%

power to show noninferiority of oral switch as compared to standard intravenous antibiotic therapy.

Setting

Trials are ongoing at the time of publication in 28 university hospitals, 14 non university hospitals, 3 private hospitals, and 1 military hospital, all in France. The planned duration of the project is 67 months: 60 months for recruitment, and 7 months for maximal follow-up. The first patient was enrolled on February 29, 2016. End of recruitment is planned on February 28, 2021. At the time of submission, 96 patients have been included in the RODEO 1 trial (staphylococci) and 190 in the RODEO 2 trial (streptococci/enterococci).

Participants

Eligibility criteria

Patients will be considered for inclusion in a trial if they have a left-sided IE and are in a stable condition after an initial course of at least 10 days of intravenous antibiotic therapy. Full eligibility criteria for both trials are listed in Table 1. Most inclusion or non-inclusion criteria are common to both trials, apart from microbiological diagnosis.

Study recruitment

To better coordinate inclusions, only one department is open in each recruiting centre. All but one are in the Infectious Diseases Unit. Potential participants are identified at the time they are hospitalized and receive IV antibiotic therapy for left-sided IE in one of the participating centres. Patients who meet selection criteria receive a brief study presentation and full participant information sheet by a clinician. After selection criteria confirmation and answering to patient questions about the trial, written informed consent is obtained. Baseline data are collected following consent.

Randomisation

Randomisation takes place between Day 10 and Day 28 after initiation of the IV antibiotic therapy (and at least 10 days of IV conventional antibiotic treatment after valvular surgery, if performed), once the patient fulfils the inclusion criteria without having non-inclusion criteria and at least 15 days of remaining antibiotic therapy. In each trial, participants are randomly assigned in a 1:1 ratio to experimental group (switch to oral antibiotic treatment) or standard treatment (continuation of IV antibiotic treatment). Randomisation is carried out with stratification on whether or not the patient underwent valvular surgery for the control of the current IE episode. There is one random computer-generated sequence for each trial. Centralised randomisation is performed using a secure web-based randomisation system.

Blinding

Patients and care providers are not blinded for pragmatic reasons (oral versus intravenous treatment).

Nevertheless, this potential bias is counterbalanced by the objectivity of primary outcome assessment (described below) and the presence of an independent blinded Endpoint Committee (EC). The EC is composed of one specialist in infectious diseases, one cardiologist and one microbiologist with expertise in IE management, research methodology and experience with clinical trials. The EC will review each suspected case in order to classify the primary outcome. Adjudication occurs after patients have completed their follow-up. Any disagreements among the EC members will be resolved during conference calls. All decisions made by the Committee are final.

Study interventions

All patients initially receive an IV antibiotic therapy during 10 to 28 days before being randomised if they fulfil the eligibility criteria. The choice of which IV antibiotic agents are used and the expected total duration of antibiotic therapy, from 4 to 6 weeks, should be consistent with the 2015 European Society of Cardiology (ESC) guidelines (3), and is under

the responsibility of the physician in charge of the patient. Only patients who still require at least 14 days of treatment for their IE will be randomised.

Experimental group:

Patients switch from initial IV antibiotic therapy to oral antibiotic therapy for the remaining duration of the treatment.

For left-sided IE due to multi-susceptible *Staphylococcus sp.*, patients ≤ 70 kg receive levofloxacin 500 mg once daily in combination with rifampin 600 mg once daily; patients > 70 kg receive levofloxacin 750 mg once a day in combination with rifampin 900 mg once a day, as proposed for prosthetic joint infections (11).

For left-sided IE due to multi-susceptible *Streptococcus sp. o*r *Enterococcus sp* (i.e susceptible to amoxicillin with a minimal inhibitory concentration (MIC) ≤ 0.5mg/L), patients ≤ 70 kg receive amoxicillin 1500 mg three times daily and patients > 70 kg receive amoxicillin 2000 mg three times daily.

If an adverse event leads to discontinuation of one antibiotic, the physician in charge of the patient will choose another oral antibiotic agent according to susceptibility testing. The patient will be classified as non-compliant with the strategy if a switch back to IV treatment is needed faced with the impossibility of finishing the remaining oral treatment period.

Control group

Patients continue IV antibiotic therapy for the remaining duration of treatment.

Study outcomes

Primary outcome

The primary efficacy outcome measure is the occurrence of treatment failure within 3 months after the end of the antibiotic treatment. Treatment failure is a composite outcome and is reached once a patient meets at least one of: 1/ Death from any cause; 2/ Symptomatic embolic events defined as secondary osteo-articular, splenic, brain or other symptomatic localization after randomisation. Silent embolic events will not be included; 3/ Unplanned

valvular surgery defined as cardiac surgery not planned before randomisation. Surgery due to sterile pericardial effusion or hemorrhage is, however, not included in this end point; 4/ Microbiological relapse (with the primary pathogen) defined as any blood culture positive yielding the same *Staphylococcus sp.* isolate or the same *Streptococcus sp. or Enterococcus sp.* isolate, as the one responsible for the initial episode of endocarditis (i.e. same species, same antibiotic susceptibility profile, the realization of genotypic testing is not mandatory and left to the discretion of investigator).

Failures will be confirmed at the end of the follow-up by an independent endpoint adjudication committee, blinded from group allocation.

We also defined a primary safety outcome of all-cause mortality at day 30 after randomisation which will be analysed after recruitment of one third and two thirds of patients within each trial.

Secondary outcomes

The following variables will be compared between allocation groups as secondary outcomes:

1. As advised for composite outcomes, each component of the primary outcome will also be considered independently.
2. Treatment failure within 6 months after the end of the antibiotic treatment.
3. New infection defined as the recurrence of positive blood cultures with a different pathogen to initial isolate sample within 3 and 6 months after the end of antibiotic therapy.
4. Outcome assessed by echocardiography

Ultrasound examinations will measure: left ventricular ejection fraction, apparition, increase or decrease of the following items: vegetation, abscess, perforation, fistula, dehiscence of a prosthetic valve. A control echocardiography will be performed at the end of antibiotic treatment, at 3 months and 6 months after the end of antibiotic treatment.

5. Catheter related adverse events (AE) and healthcare acquired infections as defined:

- Catheter-related AE: infectious (e.g. catheter-related bacteraemia) or non-infectious catheter-related complications (e.g. extravasation, thrombophlebitis)

- Other healthcare-acquired infections, including urinary tract infections, pneumonia, surgical site infection, *Clostridium difficile* infections

6. Quality of life

We will assess patient's quality of life at the end of antibiotic treatment, at 3 months and 6 months after the end of antibiotic treatment, using the EuroQol Five Dimensions (EQ5D3L)

7. Antibiotic modification

All change regarding antibiotic treatment administered will be recorded (drug, dose or duration). We will assess whether there is a need for a return to IV antibiotic in the experimental (oral switch) group.

8. Compliance with oral antibiotic treatment

The assessment of compliance with oral antibiotic treatment will be carried out at each visit during the treatment period by 2 combined methods: through a "patient leaflet" which will permit to note take/omissions of treatment, filled by the clinician during hospitalization, and by the patient or his caregivers after returning home; and through the return of the treatments' boxes to the pharmacy of the investigational site, thus allowing a pill count.

9. Economic outcomes

The difference in costs (and length of hospital stays) will be computed from the healthcare system viewpoint between each new strategy of left-sided IE management (depending on the bacteria involved) and the real-life situation. The budget impact of the diffusion of each new strategy will be computed on a three-year timeframe. Incremental cost-utility ratios will be computed to assess the clinical and economic non-inferiority of the two new strategies.

Study procedures

All patients will be followed for a 6-month period following the end of antibiotic treatment. Follow-up is planned as follows: a visit at baseline or Day 1 for randomisation (which is performed between day 10 and day 28 following the start of IV antibiotic therapy), one visit per week during the remaining antibiotic treatment duration, one visit at the end of antibiotic treatment, and one visit at 14 days, 6 weeks, 3 and 6 months following the end of antibiotic treatment (Figure 1 and 2).

Once a subject will be randomized in the study, every reasonable effort will be make to follow the subject for the complete study period even if there is a deviation from the intervention protocols, an early discontinuation of study treatment or if a participant misses one follow-up visit. If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized. All subjects who discontinue study treatment will be encouraged to complete all remaining scheduled visits and procedures.

Data management

Data is recorded on study-specific electronic case report forms (eCRFs) via an electronic data capture system (eCRF model is available on request to the principal investigator). To maintain participants' anonymity, CRFs are identified only by a patient number and initials. All records that contain patient names or other identifying information will be stored separately from the study records in each centre and can be identified only by the patient number and initials.

Sample size

Sample size calculations are based on a null hypothesis of H0: $\pi 2 - \pi 1 \geq$ delta (ie, inferior); where $\pi 1$ is the proportion of patients expected to experience failure in the intravenous group, $\pi 2$ is the proportion in the oral switch group, and the non-inferiority margin delta is 10%. The alternative hypothesis is $\pi 2 - \pi 1 <$ delta (ie, noninferior).We considered each pathogen separately to ensure that we will have sufficient statistical power to explore non-inferiority of

oral switch for staphylococci as well as for streptococci/enterococci. Thus, for each pathogen, *Staphylococcus sp*. and *Streptococcus/Enterococcus sp*., we assumed an expected failure proportion of 10% (3,17,18), taking into account the fact that we will only enrol patients who have a favourable outcome after the first 10 days of IE treatment), a non-inferiority margin of 10%, a one-sided Type I error of 2.5%, and a power of 80%. The number of subjects required is estimated at 145 evaluable subjects per group, thus a total of 290 randomised patients. It is expected that approximately 10% of patients will not be available for the per-protocol outcome assessment, leading to a total of 324 patients to be enrolled, to be sufficiently powered for the per-protocol analysis. The total required sample size is thus 648 patients: 324 patients for the *Staphylococcus sp.* IE (RODEO 1 trial), and 324 further patients with *Streptococcus/Enterococcus sp*. IE (RODEO 2 trial).

Statistical analyses

Statistical analyses will be conducted in both intention to treat (ITT) and per protocol (PP) methodology as recommended for non-inferiority trials. The PP population will exclude patients for whom there is a clear major protocol violation as defined during a blind review prior to any statistical analysis. Analyses will be conducted using two-sided significance tests at the 5% significance level. A participant flow diagram will be reported. Group characteristics at baseline will be studied with descriptive statistics. No statistical tests will be performed on baseline characteristics. For each trial, the rate of the primary outcome will be estimated within each intervention group. Difference of failure proportions between oral switch (p2) and entire parenteral treatment (p1) for the end of antibiotic treatment will be estimated. We will declare oral switch to be non-inferior to parenteral treatment if the upper bound of the one-sided 97.5% CI is less than 10%.

This analysis will be performed in both the ITT and PP populations. Subgroup analyses will be performed considering the two strata defined by requirement of valvular surgery before

randomisation or not. Missing data will not be replaced except for the primary outcome on ITT population. Missing value will be considered a failure whatever the randomised group. A sensitivity analysis will be performed excluding patients with missing primary outcome (complete-case analysis). Potential post-hoc sensitivity analyses will be performed.

Statistical analysis will be first performed separately for each trial i.e. for staphylococci IE and streptococci-enterococci IE. Then, according to the results, we will consider a pooled analysis.

Concerning secondary objectives, the statistical analysis will be the same as for the primary outcome for the components of the primary outcome. Proportions of abnormalities will be compared using chi-square tests for echocardiographic outcomes.

Healthcare-acquired infection proportions and catheter related non-infectious adverse event proportions will be estimated per group and compared using chi-square tests or Fisher exact tests.

Change in health-related quality of life will be analyzed considering a linear mixed-effects regression model taking into account repeated measures for a given patient.

Descriptive statistics of compliance with oral therapy will be provided in the experimental group. Analysis will be performed in SAS 9.4 (SAS institute, Cary NC) and R 3.3 (19) softwares (or latest versions).

Economic evaluation

From the data of three recruiting centres, cost analysis will evaluate, from the healthcare system viewpoint, which strategy between the oral switch (after an IV period of induction) or the IV antibiotic treatment (reference strategy) is less costly.

On this basis, the budget impact on the healthcare system of the diffusion of the oral switch strategy will be computed using a budget impact analysis on a three-years' timeframe.

Direct medical costs will be assessed from the healthcare system perspective in both groups and during the whole induction and follow-up period i.e. 6 months after the end of treatment. For each patient, we will collect the healthcare resources used both in the hospital setting and primary care services. This covers the initial hospital stay, subsequent hospital stays due to complications/infections, rehabilitation stay, and antibiotics delivered in primary care. Data will be collected from the local hospital discharge databases of three centres (for hospitalizations) and from the CRF of all patients (rehabilitation care and antibiotics).

Using data from all recruiting centres, a cost-utility analysis will be performed to compute an incremental cost-utility ratio "cost per QALY gained". QALY will be computed from the survival data and utility scores obtained from the responses to the questionnaire EQ5D-3L.

Data monitoring

Clinical research associates will ensure that patient inclusion, data collection, registry and rapport are in accordance with the standard operating procedures of the sponsor and the French Good Clinical Practices. They will verify during the quality control visits (at least once a year per centre), in collaboration with investigators: the presence of written consent, compliance with the research protocol, the quality of pre-specified data collected in the case report form and its consistency with the 'source' documents and the management of treatments used.

Moreover, a Data Safety Monitoring Committee (DSMC) comprising two independent clinicians and one independent statistician meets approximately every 6 months to discuss any issues related to patient safety. All serious adverse events will be reviewed by the DSMC as well as interim analysis of the primary safety outcome. Interim analyses of all-cause mortality at 30 days following randomisation will be performed after recruitment of one third and two thirds of patients within each trial. Early stopping rule will be to stop the trial for safety concerns if a P value <0.01 is observed. The role and responsibilities of the DSMC are set out

in a written charter. The DSMC provides written recommendations to the trial steering committee following each meeting.

Ethics and dissemination

This protocol was approved by local ethics research committee (CPP TOURS - Region Centre - Ouest 1, 2015-R26, February 23, 2016). An agreement from the French national drug safety agency (ANSM) has also been obtained.

In conformity with the Declaration of Helsinki, all participants sign a written informed consent form that describes this study and provides sufficient information for patients to make an informed decision about their participation. Consent is obtained from patients before they undergo any study procedure. Participants may withdraw from the study at any time during the clinical trial without any impact on their care. In that event, data collected prior to participant withdrawal will be used in the trial analysis. Sponsor of the study may audit trial conduct as deemed appropriate. A formal amendment to the local research ethics committee will be required for any amendments to the study protocol which may impact the conduct of the study, or the potential safety of, or benefits to patients. If needed, an amendment will also be required from the National regulatory Agency for Security of Medicines and healthcare products (ANSM). Any protocol amendments will be communicated to investigators and oversight authority but also to trial participants and registries, if deemed necessary. The 8th amendment was the most recently approved, on December 17, 2018.

Reports will follow international guidelines: CONSORT Statement and Extension of the CONSORT Statement for reporting of non-inferiority and equivalence trials. Research findings will be submitted for publication in peer-reviewed journals regardless of whether or not they are statistically significant. Authors will be individuals who have made key contributions to study design and conduct. Trial findings will also be submitted for

presentation at scientific meetings. The study findings will also be presented at relevant national and international conferences.

Patient and public involvement

Patients and public were not involved in the study design, recruitment or conduction of the study. The burden of intervention was assessed by representatives of patient associations participating in the ethical committee. Participants may obtain access to the final results of the study through the local principal investigator.

Discussion

Several recent reviews point out the necessity of high-quality clinical studies in order to improve the level of evidence for the IE management (3–5). The RODEO trials aim to respond to this demand.

Iversen *et al.* in the POET study have recently documented, in a first randomised open-label controlled trial, that a partial oral antibiotic treatment in left-sided IE was non inferior to continued IV treatment and was not associated with unfavourable outcome (16). However, this study had some limitations which could be addressed in the RODEO study. First, strict inclusion criteria resulted in a large number of exclusions among screened patients (1,554 out of 1,954). We expect that the broader inclusion criteria of the RODEO project will lead to better external validity of the results. Second, unlike the POET study, the oral treatment regimen in our study will be more homogeneous, and closely controlled as the investigational products will be provided and controlled by the trial sponsor. Another limitation in the POET study was the potential bias of merging staphylococci, streptococci, and enterococci for analysis. Indeed, *S. aureus* is regularly isolated as a risk factor for poor outcome in IE (2,17,20), while IE due to streptococci with low minimal inhibitory concentrations (MIC) for amoxicillin could be treated with a short course of IV antibiotic treatment (21).

The RODEO trials will be the biggest multicentre randomised controlled trials to assess non-inferiority of oral switch of antibiotic therapy as compared to entirely intravenous antibiotic therapy in adult patients with left-sided IE due to Gram positive cocci (staphylococci for RODEO 1, streptococci and enterococci for RODEO 2).

If the non-inferiority is confirmed, this strategy could be a way to improve patients' quality of life and reduce IE associated healthcare costs. In order to evaluate this point, a medico-economic evaluation will be conducted alongside the trial.

The pragmatic design of these studies with wide eligibility criteria will permit to evaluate properly the medico-economic analysis, close to the real-life situation.

In the RODEO trials, oral regimens are simplified in the experimental arm, contrarily to the recent POET trial which proposed many different oral combinations (16). Several reasons explain that choice. Firstly, the homogeneity of treatment will be easier to interpret in each of the experimental arm. The combination therapy with rifampicin and quinolones has already been approved in other deep infections due to staphylococci (22,23). For streptococcal IE, oral amoxicillin has been recommended with reassuring results (8,13). Then, this is adapted to the French epidemiology of infective endocarditis with a relative paucity of resistant bacteria (2,20). Therefore, precaution will have to be taken in the extrapolation of the results, notably for IE due to staphylococci resistant to quinolones and enterococci, as MIC are frequently over 0.5 mg/L (24).

The expected non-inferiority of the experimental arm should help to modify the actual recommendations for IE management. Some retrospective studies had already pointed out the interest of oral switch of antibiotic treatment in IE (6,13,15), and a first randomised assay found the same results (16). The RODEO trials will possibly confirm these conclusions and try to demonstrate a potential medico-economic benefit to this strategy.

Their design will also permit to give robust conclusions for both streptococci and staphylococci IE with appropriate power.

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Author contributions

LB conceived and designed the final trial protocol. AC is responsible for the methodological design of the study and designed the protocol for statistical analysis. SBH is responsible for the economic evaluation. AL, LB and AC wrote the first draft of the manuscript. LB, PT, JPB, XD, BH and JLM are members of the scientific committee. AL, LB, PT, JPB, XD, BH, JLM and members of the RODEO study group will be investigators and will recruit patients and conduct the trial. All authors read, reviewed and approved the final manuscript.

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Competing interests None.

Ethics approval Tours Research Ethics Committee (CPP TOURS - Region Centre - Ouest 1, 2015-R26, 23/02/2016).

Data sharing statement

There are no plans to grant public access to the full protocol, participant-level data or statistical code. Data from the RODEO trials is stored by the promotor of the trial. Data and the personal identifiers are stored separately and a special permit is required for access to the data. Data can be available on request for academic researchers when it have been analysed and published. Qualified researchers can ask for data sharing by the first author LB after the study finalization.

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Table 1: Eligibility criteria for RODEO 1 and RODEO 2 trials

Inclusion criteria
For both trials
Diagnosis of definite left-sided IE according to Duke criteria (3) on native or prosthetic valve
Age ≥18 year old
Appropriate parenteral antibiotic treatment received for at least 10 days
In case of valvular surgery, appropriate parenteral antibiotic treatment received for at least 10 days after surgery
Planned duration of antibiotics of at least 14 days at the time of randomisation (ensuring to have at least 14 days of oral therapy remaining in the experimental group)
Absence of fever (temperature < 38°C) at each time point during the last 48 hours (at least two measures/day) at the time of randomisation
Negative blood cultures for at least 5 days at the time of randomisation
Informed, written consent obtained from patient
Patient covered by or having the rights to French social security
For RODEO 1: left-sided *Staphylococcus* IE
Left-sided IE due to *Staphylococcus* sp. (*S. aureus* or coagulase negative staphylococci) susceptible to levofloxacin and rifampicin
For RODEO 2: left-sided *Streptococcus* IE
Left-sided IE due to *Streptococcus*/*Enterococcus* sp. susceptible to amoxicillin (minimal inhibitory concentrations MIC ≤ 0.5 mg/l)
Non-inclusion criteria
For both trials
Body mass index <15 kg/m² or > 40 kg/m²
Inability or unwillingness to take oral treatment for any reason (digestive intolerance, significant malabsorption) at the time of randomisation
Absence of an entourage to support and watch for him/her at discharge
Expected difficulties regarding compliance with oral antibiotic treatment or follow-up (e.g. severe cognitive impairment, severe psychiatric disease...)
Valvular surgery planned within the next 6 months
Presence of cardiac devices (pace-maker, implantable cardiac defibrillator) with suspected device-related IE without removal of the device
Breast feeding or pregnancy, or women on childbearing age without effective contraception

Expected duration of follow-up < 7 months at the time of randomisation (e.g. expected life expectancy < 7 months, patient living abroad...)
Past medical history of IE in the last 3 months
Other infection requiring parenteral antibiotic therapy after the randomisation
Inclusion in another interventional clinical trial
For RODEO 1: left-sided *Staphylococcus* IE
Glomerular filtration rate < 50 ml/min/1,73m2 for patients with *Staphylococcus* sp (*S. aureus* or coagulase negative staphylococci) infection
Contra-indication to oral antibiotics administered in the experimental arm (i.e. fluoroquinolones or rifampin) - including anticipated non-manageable drug interactions with rifampicin, and allergy or severe intolerance
Taking of an estrogen-progesterone treatment interacting with rifampicin
For RODEO 2: left-sided *Streptococcus* IE
Glomerular filtration rate < 30 ml/min/1.73m2 for patients with *Streptococcus/Enterococcus* sp. infection
Contra-indication to oral antibiotics administered in the experimental arm (i.e. amoxicillin) - including allergy or severe intolerance

Figure 1: Study design

IE: Infective Endocarditis. IV: intra-veinous

Figure 2: Study schedule

*Clinical examination will collect the following information: body temperature, blood pressure, heart murmur (new or modified), any infectious site, list and tolerance of any drug, with a special focus on digestive symptoms, rash, neuropsychiatric complaints.

**Residual concentration of ATB is realized only for patients randomized in “oral therapy” group.

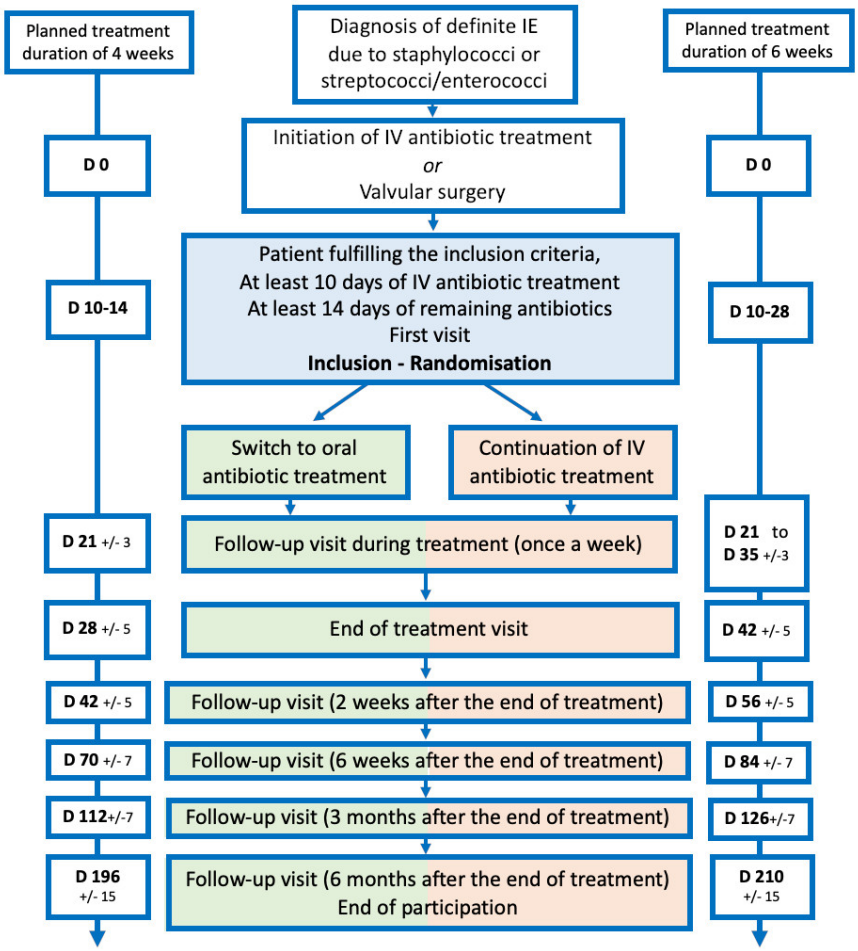

Figure 1: Study design
IE: Infective Endocarditis. IV: intra-veinous

90x90mm (300 x 300 DPI)

	START OF IV ANTIBIOTIC THERAPY/OR VALVULAR SURGERY (D0)	Visit 1	Per treatment visit (once a week thus from 2 to 4 visits according to the remaining treatment duration at randomisation)	After the end of treatment visit (4 visits for each patient i.e 14 days, 1.5, 3 and 6 months after the end of antibiotic treatment)
Patient information		X		
Criteria for inclusion / non-inclusion		X		
Signature of consent		X		
Randomisation		X		
Socio-demographic characteristics		X		
Clinical information				
History of IE		X		
Clinical examination*		X	X	X
Questionnaire				
Quality of life (EQ5D3L)		X	X (at the end of antibiotic treatment)	X (at 3 months and 6 months after the end of antibiotic treatment)
Compliance with antibiotic treatment			X	
Laboratory tests				
Complete Blood Count		X	X	X
C-reactive protein		X	X	X
Liver function tests Albuminemia, glomerular filtration rate		X	X	
Blood cultures (2 bottles, 10 mL/bottle)		X	X	X
Residual concentration of ATB**			X (at visit 2)	
Blood sample for biological collection		X		
Adverse events and concomitant medications			X	X
Echocardiography		X	X (at the end of antibiotic treatment)	X (at 3 months and 6 months after the end of antibiotic treatment)

Figure 2: Study schedule

*Clinical examination will collect the following information: body temperature, blood pressure, heart murmur (new or modified), any infectious site, list and tolerance of any drug, with a special focus on digestive symptoms, rash, neuropsychiatric complaints.

**Residual concentration of ATB is realized only for patients randomized in "oral therapy" group.

106x60mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	19
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-4 & 21
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	2

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11, 13, 18, 21
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8-9
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	9
Objectives	#7	Specific objectives or hypotheses	9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11-12 & 26-27
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-12 & 28-29

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	12-13
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	15
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	26-27
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14-15 & 28-29
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15-16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15 & 17-18
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17-18
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18-19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	19
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results	19

		databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	22
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Available on request
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

BMJ Open

Oral switch versus standard intravenous antibiotic therapy in left-sided endocarditis due to susceptible staphylococci, streptococci or enterococci (RODEO): a protocol for two open-label randomised controlled trials

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Oral switch versus standard intravenous antibiotic therapy in left-sided endocarditis due to susceptible staphylococci, streptococci or enterococci (RODEO): a protocol for two open-label randomised controlled trials

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ABSTRACT

Introduction

Left-sided infective endocarditis (IE) is a serious infection with a heavy burden for patients and healthcare system. Oral switch after initial intravenous antibiotic therapy may reduce costs and improve patients' discomfort without increasing unfavourable outcomes. We describe the methodology of two simultaneously conducted open-label randomised trials aiming to assess non-inferiority of oral switch as compared to entirely intravenous antibiotic therapy for the treatment of left-sided IE.

Methods and analysis

Two simultaneous multicentre open-label prospective randomised trials assessing non inferiority of oral switch during antibiotic treatment as compared to entirely intravenous therapy in patients with left-sided IE are ongoing. One trial is dedicated to left-sided IE caused by multi-susceptible staphylococci (RODEO-1) and the other is dedicated to left-sided IE caused by susceptible streptococci or enterococci (RODEO-2). It is planned to randomise 324 patients in each trial after an initial course of at least 10 days of intravenous antibiotic therapy either to continue intravenous antibiotic therapy or to switch to oral antibiotic therapy. The primary outcome is treatment failure within 3 months after the end of antibiotic treatment, a composite outcome defined by all-cause death and/or symptomatic embolic events and/or unplanned valvular surgery and/or microbiological relapse (with the primary pathogen). Secondary outcomes include patient quality of life, echocardiographic outcome, costs and efficiency associated with IE care. Statistical analysis will be performed with a non-inferiority margin of 10% and a one-sided 2.5% type I error.

Ethics and dissemination:

Written informed consent will be obtained from all participants. This study was approved by Tours Research ethics committee (CPP TOURS-Region Centre-Ouest 1, 2015-R26, 23/02/2016). Study findings will be published in peer-reviewed journals and disseminated through presentation at relevant national and international conferences.

Registration details:

The trials are registered with the European Clinical Trials Database (EudraCT Number: 2015-002371-16) and on clinicaltrials.gov (NCT02701608 and NCT02701595).

Keywords:

Infective endocarditis, oral administration, randomized controlled trial, anti-bacterial agents, adult

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ARTICLE SUMMARY

Strengths and limitations of this study

- RODEO 1-2 trials are multicentre randomised controlled trials appropriately designed and powered to assess non-inferiority of oral switch of antibiotic therapy as compared to entirely intravenous antibiotic therapy in patients with left-sided infective endocarditis
- An economic evaluation, including a cost analysis, a cost-utility analysis and a budget impact analysis, will be conducted alongside the trials.
- In these trials, few regimens are proposed for oral switch, in line with local epidemiology with a relative paucity of resistant bacteria, thus allowing a better homogeneity in the analysis.
- Limitation due to the open-label design of those randomised trials will be limited by the use of a blinded committee to adjudicate the primary outcome. Primary outcome will be measured at 3 months in order to decrease the risk of lost-to-follow-up, the outcome at 6 months being measured as a secondary objective.

Introduction

Infective endocarditis (IE) is a serious infectious disease with a heavy burden for patients and healthcare system (1). In France, median length of hospital stay for patients with IE is 43 days (2) partly linked to the prolonged intravenous (IV) antibiotic therapy recommended by international guidelines (between 4 and 6 weeks in most situations) (3). Current guidelines for IE management are mostly based on expert opinion, *in vitro* studies, animal experiments, or clinical studies performed before the 90's, as very few randomised studies have been conducted (4,5). The only exception to the golden rule of 'IV treatment for all IE' is right-sided IE due to meticillin-susceptible *Staphylococcus aureus* (MSSA), in which the efficacy of an oral combination of ciprofloxacin and rifampicin has been validated in one randomised trial which only included 44 patients (6). Most experts acknowledge that the pharmacodynamic and pharmacokinetic characteristics of antibiotics such as amoxicillin, fluoroquinolones and rifampicin allow a high level of efficacy in the treatment of severe infections due to *S. aureus*, including IE, when orally administrated after an initial phase with adequate IV antibiotic therapy (7–12). A recent systematic review of oral therapy for the treatment of right- or left-sided IE found only one observational study reporting 80% cure rate with oral amoxicillin in 15 cases of streptococcal left-sided IE (13). Two recent studies regarding the management of IE in France showed that a switch from IV to oral antibiotics is feasible when patients with left-sided *Staphylococcus* or *Streptococcus* IE are stable after an initial course of IV antibiotic treatment, with or without valvular surgery (14,15). These practices have not been associated with unfavourable outcome, while significantly reducing the duration and cost of hospitalization, the risk of nosocomial infection, and patients' discomfort. A first randomised trial recently found non-inferiority of partial oral treatment as compared to continued intravenous antibiotic treatment in IE due to Gram-positive cocci whatever its species (16). Other well-designed randomised controlled trials are however

needed to confirm the clinical non-inferiority of this strategy in IE due to most common bacteria (multisusceptible staphylococci, susceptible streptococci or enterococci), specifying for each group of species. Addressing these bacteria in two simultaneously performed trials would ensure an optimal recruitment, reduce cost of research, and argue for/against oral switch in the majority of IE patients. The RODEO project corresponds to two pragmatic open-label randomised trials assessing non inferiority of oral switch during antibiotic treatment as compared to entirely intravenous standard-therapy in patients with left-sided IE. One trial is dedicated to left-sided IE caused by multi-susceptible *Staphylococcus* and the other dedicated to left-sided IE caused by multi-susceptible *Streptococcus* including *Enterococcus*.

Methods and analysis

Study hypothesis

We hypothesise that oral switch for antibiotic therapy is non-inferior to entirely IV antibiotic therapy in the treatment of left-sided IE as assessed by the proportion of patients with treatment failure within 3 months after the end of antibiotic treatment.

Study design

RODEO project comprises two simultaneously performed nationwide, multi-centre, open-label non inferiority randomised controlled trials comparing oral switch with entirely intravenous antibiotic therapy in patients with left-sided IE and an initial course of at least 10 days of effective intravenous antibiotic therapy. One trial is dedicated to left-sided IE caused by multi-susceptible *Staphylococcus* (RODEO-1 trial) and the other dedicated to left-sided IE caused by multi-susceptible *Streptococcus* including *Enterococcus* (RODEO-2 trial). Both trials are based on the same protocol provided below. Nevertheless, they are considered as two distinct trials, and sample sizes were calculated separately so that each trial has 80%

power to show noninferiority of oral switch as compared to standard intravenous antibiotic therapy.

Setting

Trials are ongoing at the time of publication in 28 university hospitals, 14 non university hospitals, 3 private hospitals, and 1 military hospital, all in France. The planned duration of the project is 67 months: 60 months for recruitment, and 7 months for maximal follow-up. The first patient was enrolled on February 29, 2016. End of recruitment is planned on February 28, 2021. At the time of submission, 96 patients have been included in the RODEO 1 trial (staphylococci) and 190 in the RODEO 2 trial (streptococci/enterococci).

Participants

Eligibility criteria

Patients will be considered for inclusion in a trial if they have a left-sided IE and are in a stable condition after an initial course of at least 10 days of intravenous antibiotic therapy. Full eligibility criteria for both trials are listed in Table 1. Most inclusion or non-inclusion criteria are common to both trials, apart from microbiological diagnosis. Microbiological analyses are not centralised but all participating microbiological wards are certified ISO15-189 and follow the current CASFM/EUCAST guidelines (17). Drug-susceptibility testing follow the EUCAST disk diffusion method (18) and minimal inhibitory concentration (MIC) are determined by broth microdilution or calibrated diffusion strips.

Study recruitment

To better coordinate inclusions, only one department is open in each recruiting centre. All but one are in the Infectious Diseases Unit. Potential participants are identified at the time they are hospitalized and receive IV antibiotic therapy for left-sided IE in one of the participating centres. Patients who meet selection criteria receive a brief study presentation and full

participant information sheet by a clinician. After selection criteria confirmation and answering to patient questions about the trial, written informed consent is obtained. Baseline data are collected following consent.

Randomisation

Randomisation takes place between Day 10 and Day 28 after initiation of the IV antibiotic therapy (and at least 10 days of IV conventional antibiotic treatment after valvular surgery, if performed), once the patient fulfils the inclusion criteria without having non-inclusion criteria and at least 15 days of remaining antibiotic therapy. In each trial, participants are randomly assigned in a 1:1 ratio to experimental group (switch to oral antibiotic treatment) or standard treatment (continuation of IV antibiotic treatment). Randomisation is carried out with stratification on whether or not the patient underwent valvular surgery for the control of the current IE episode. There is one random computer-generated sequence for each trial. Centralised randomisation is performed using a secure web-based randomisation system.

Blinding

Patients and care providers are not blinded for pragmatic reasons (oral versus intravenous treatment).

Nevertheless, this potential bias is counterbalanced by the objectivity of primary outcome assessment (described below) and the presence of an independent blinded Endpoint Committee (EC). The EC is composed of one specialist in infectious diseases, one cardiologist and one microbiologist with expertise in IE management, research methodology and experience with clinical trials. The EC will review each suspected case in order to classify the primary outcome. Adjudication occurs after patients have completed their follow-up. Any disagreements among the EC members will be resolved during conference calls. All decisions made by the Committee are final.

Study interventions

All patients initially receive an IV antibiotic therapy during 10 to 28 days before being randomised if they fulfil the eligibility criteria. The choice of which IV antibiotic agents are used and the expected total duration of antibiotic therapy, from 4 to 6 weeks, should be consistent with the 2015 European Society of Cardiology (ESC) guidelines (3), and is under the responsibility of the physician in charge of the patient. Only patients who still require at least 14 days of treatment for their IE will be randomised.

Experimental group:

Patients switch from initial IV antibiotic therapy to oral antibiotic therapy for the remaining duration of the treatment.

For left-sided IE due to multi-susceptible *Staphylococcus sp.*, patients ≤ 70 kg receive levofloxacin 500 mg once daily in combination with rifampin 600 mg once daily; patients > 70 kg receive levofloxacin 750 mg once a day in combination with rifampin 900 mg once a day, as proposed for prosthetic joint infections (11).

For left-sided IE due to multi-susceptible *Streptococcus sp. o*r *Enterococcus sp* (i.e susceptible to amoxicillin with a MIC ≤ 0.5mg/L), patients ≤ 70 kg receive amoxicillin 1500 mg three times daily and patients > 70 kg receive amoxicillin 2000 mg three times daily.

If an adverse event leads to discontinuation of one antibiotic, the physician in charge of the patient will choose another oral antibiotic agent according to susceptibility testing. The patient will be classified as non-compliant with the strategy if a switch back to IV treatment is needed faced with the impossibility of finishing the remaining oral treatment period.

Control group

Patients continue IV antibiotic therapy for the remaining duration of treatment.

Study outcomes

Primary outcome

The primary efficacy outcome measure is the occurrence of treatment failure within 3 months after the end of the antibiotic treatment. Treatment failure is a composite outcome and is reached once a patient meets at least one of: 1/ Death from any cause; 2/ Symptomatic embolic events defined as secondary osteo-articular, splenic, brain or other symptomatic localization after randomisation. Silent embolic events will not be included; 3/ Unplanned valvular surgery defined as cardiac surgery not planned before randomisation. Surgery due to sterile pericardial effusion or hemorrhage is, however, not included in this end point; 4/ Microbiological relapse (with the primary pathogen) defined as any blood culture positive yielding the same *Staphylococcus sp.* isolate or the same *Streptococcus sp. or Enterococcus sp.* isolate, as the one responsible for the initial episode of endocarditis (i.e. same species, same antibiotic susceptibility profile, the realization of genotypic testing is not mandatory and left to the discretion of investigator).

Failures will be confirmed at the end of the follow-up by an independent endpoint adjudication committee, blinded from group allocation.

We also defined a primary safety outcome of all-cause mortality at day 30 after randomisation which will be analysed after recruitment of one third and two thirds of patients within each trial.

Secondary outcomes

The following variables will be compared between allocation groups as secondary outcomes:

1. As advised for composite outcomes, each component of the primary outcome will also be considered independently.
2. Treatment failure within 6 months after the end of the antibiotic treatment.
3. New infection defined as the recurrence of positive blood cultures with a different pathogen to initial isolate sample within 3 and 6 months after the end of antibiotic therapy.

4. Outcome assessed by echocardiography

Ultrasound examinations will measure: left ventricular ejection fraction, apparition, increase or decrease of the following items: vegetation, abscess, perforation, fistula, dehiscence of a prosthetic valve. A control echocardiography will be performed at the end of antibiotic treatment, at 3 months and 6 months after the end of antibiotic treatment.

5. Catheter related adverse events (AE) and healthcare acquired infections as defined:

- Catheter-related AE: infectious (e.g. catheter-related bacteraemia) or non-infectious catheter-related complications (e.g. extravasation, thrombophlebitis)
- Other healthcare-acquired infections, including urinary tract infections, pneumonia, surgical site infection, *Clostridium difficile* infections

6. Quality of life

We will assess patient's quality of life at the end of antibiotic treatment, at 3 months and 6 months after the end of antibiotic treatment, using the EuroQol Five Dimensions (EQ5D3L)

7. Antibiotic modification

All change regarding antibiotic treatment administered will be recorded (drug, dose or duration). We will assess whether there is a need for a return to IV antibiotic in the experimental (oral switch) group.

8. Compliance with oral antibiotic treatment

The assessment of compliance with oral antibiotic treatment will be carried out at each visit during the treatment period by 2 combined methods: through a "patient leaflet" which will permit to note take/omissions of treatment, filled by the clinician during hospitalization, and by the patient or his caregivers after returning home; and through the return of the treatments' boxes to the pharmacy of the investigational site, thus allowing a pill count.

9. Economic outcomes

The difference in costs (and length of hospital stays) will be computed from the healthcare system viewpoint between each new strategy of left-sided IE management (depending on the bacteria involved) and the real-life situation. The budget impact of the diffusion of each new strategy will be computed on a three-year timeframe. Incremental cost-utility ratios will be computed to assess the clinical and economic non-inferiority of the two new strategies.

Study procedures

All patients will be followed for a 6-month period following the end of antibiotic treatment. Follow-up is planned as follows: a visit at baseline or Day 1 for randomisation (which is performed between day 10 and day 28 following the start of IV antibiotic therapy), one visit per week during the remaining antibiotic treatment duration, one visit at the end of antibiotic treatment, and one visit at 14 days, 6 weeks, 3 and 6 months following the end of antibiotic treatment (Figure 1 and 2).

Once a subject will be randomized in the study, every reasonable effort will be make to follow the subject for the complete study period even if there is a deviation from the intervention protocols, an early discontinuation of study treatment or if a participant misses one follow-up visit. If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized. All subjects who discontinue study treatment will be encouraged to complete all remaining scheduled visits and procedures.

Data management

Data is recorded on study-specific electronic case report forms (eCRFs) via an electronic data capture system (eCRF model is available on request to the principal investigator). To maintain participants' anonymity, CRFs are identified only by a patient number and initials. All records that contain patient names or other identifying information will be stored separately from the study records in each centre and can be identified only by the patient number and initials.

Sample size

Sample size calculations are based on a null hypothesis of H0: $\pi 2 - \pi 1 \geq$ delta (ie, inferior); where $\pi 1$ is the proportion of patients expected to experience failure in the intravenous group, $\pi 2$ is the proportion in the oral switch group, and the non-inferiority margin delta is 10%. The alternative hypothesis is $\pi 2 - \pi 1 <$ delta (ie, noninferior).We considered each pathogen separately to ensure that we will have sufficient statistical power to explore non-inferiority of oral switch for staphylococci as well as for streptococci/enterococci. Thus, for each pathogen, *Staphylococcus sp*. and *Streptococcus/Enterococcus sp*., we assumed an expected failure proportion of 10% (3,19,20), taking into account the fact that we will only enrol patients who have a favourable outcome after the first 10 days of IE treatment), a non-inferiority margin of 10%, a one-sided Type I error of 2.5%, and a power of 80%. The number of subjects required is estimated at 145 evaluable subjects per group, thus a total of 290 randomised patients. It is expected that approximately 10% of patients will not be available for the per-protocol outcome assessment, leading to a total of 324 patients to be enrolled, to be sufficiently powered for the per-protocol analysis. The total required sample size is thus 648 patients: 324 patients for the *Staphylococcus sp.* IE (RODEO 1 trial), and 324 further patients with *Streptococcus/Enterococcus sp*. IE (RODEO 2 trial).

Statistical analyses

Statistical analyses will be conducted in both intention to treat (ITT) and per protocol (PP) methodology as recommended for non-inferiority trials. The PP population will exclude patients for whom there is a clear major protocol violation as defined during a blind review prior to any statistical analysis. Analyses will be conducted using two-sided significance tests at the 5% significance level. A participant flow diagram will be reported. Group characteristics at baseline will be studied with descriptive statistics. No statistical tests will be performed on baseline characteristics. For each trial, the rate of the primary outcome will be

estimated within each intervention group. Difference of failure proportions between oral switch (p2) and entire parenteral treatment (p1) for the end of antibiotic treatment will be estimated. We will declare oral switch to be non-inferior to parenteral treatment if the upper bound of the one-sided 97.5% CI is less than 10%. This analysis will be performed in both the ITT and PP populations. In the ITT analysis, missing primary outcome data will be handled by assuming that patients with missing data have treatment failure whatever the randomised group (worst case single imputation, assuming data are missing not at random). A sensitivity analysis will be performed excluding patients with missing primary outcome (complete-case analysis, assuming that data are missing completely at random). Subgroup analyses will be performed considering the two strata defined by requirement of valvular surgery before randomisation or not. To assess the impact of a potential centre-effect, a sensitivity analysis of the primary outcome will be performed with a random-centre-effect model. Potential post-hoc sensitivity analyses will be performed.

Statistical analysis will be first performed separately for each trial i.e. for staphylococci IE and streptococci-enterococci IE. Then, according to the results, we will consider a pooled analysis.

Concerning secondary objectives, the statistical analysis will be the same as for the primary outcome for the components of the primary outcome. Proportions of abnormalities will be compared using chi-square tests for echocardiographic outcomes.

Healthcare-acquired infection proportions and catheter related non-infectious adverse event proportions will be estimated per group and compared using chi-square tests or Fisher exact tests.

Change in health-related quality of life will be analyzed considering a linear mixed-effects regression model taking into account repeated measures for a given patient.

No imputation of missing data will be performed for the secondary outcomes. Descriptive statistics of compliance with oral therapy will be provided in the experimental group. Analysis will be performed in SAS 9.4 (SAS institute, Cary NC) and R 3.3 (21) softwares (or latest versions).

Economic evaluation

From the data of three recruiting centres, cost analysis will evaluate, from the healthcare system viewpoint, which strategy between the oral switch (after an IV period of induction) or the IV antibiotic treatment (reference strategy) is less costly.

On this basis, the budget impact on the healthcare system of the diffusion of the oral switch strategy will be computed using a budget impact analysis on a three-years' timeframe.

Direct medical costs will be assessed from the healthcare system perspective in both groups and during the whole induction and follow-up period i.e. 6 months after the end of treatment. For each patient, we will collect the healthcare resources used both in the hospital setting and primary care services. This covers the initial hospital stay, subsequent hospital stays due to complications/infections, rehabilitation stay, and antibiotics delivered in primary care. Data will be collected from the local hospital discharge databases of three centres (for hospitalizations) and from the CRF of all patients (rehabilitation care and antibiotics).

Using data from all recruiting centres, a cost-utility analysis will be performed to compute an incremental cost-utility ratio "cost per QALY gained". QALY will be computed from the survival data and utility scores obtained from the responses to the questionnaire EQ5D-3L.

Data monitoring

Clinical research associates will ensure that patient inclusion, data collection, registry and rapport are in accordance with the standard operating procedures of the sponsor and the French Good Clinical Practices. They will verify during the quality control visits (at least once a year per centre), in collaboration with investigators: the presence of written consent,

compliance with the research protocol, the quality of pre-specified data collected in the case report form and its consistency with the 'source' documents and the management of treatments used.

Moreover, a Data Safety Monitoring Committee (DSMC) comprising two independent clinicians and one independent statistician meets approximately every 6 months to discuss any issues related to patient safety. All serious adverse events will be reviewed by the DSMC as well as interim analysis of the primary safety outcome. Interim analyses of all-cause mortality at 30 days following randomisation will be performed after recruitment of one third and two thirds of patients within each trial. Early stopping rule will be to stop the trial for safety concerns if a P value <0.01 is observed. The role and responsibilities of the DSMC are set out in a written charter. The DSMC provides written recommendations to the trial steering committee following each meeting.

Ethics and dissemination

This protocol was approved by local ethics research committee (CPP TOURS - Region Centre - Ouest 1, 2015-R26, February 23, 2016). An agreement from the French national drug safety agency (ANSM) has also been obtained.

In conformity with the Declaration of Helsinki, all participants sign a written informed consent form that describes this study and provides sufficient information for patients to make an informed decision about their participation. Consent is obtained from patients before they undergo any study procedure. Participants may withdraw from the study at any time during the clinical trial without any impact on their care. In that event, data collected prior to participant withdrawal will be used in the trial analysis. Sponsor of the study may audit trial conduct as deemed appropriate. A formal amendment to the local research ethics committee will be required for any amendments to the study protocol which may impact the conduct of the study, or the potential safety of, or benefits to patients. If needed, an amendment will also

be required from the National regulatory Agency for Security of Medicines and healthcare products (ANSM). Any protocol amendments will be communicated to investigators and oversight authority but also to trial participants and registries, if deemed necessary. The 8th amendment was the most recently approved, on December 17, 2018.

Reports will follow international guidelines: CONSORT Statement and Extension of the CONSORT Statement for reporting of non-inferiority and equivalence trials. Research findings will be submitted for publication in peer-reviewed journals regardless of whether or not they are statistically significant. Authors will be individuals who have made key contributions to study design and conduct. Trial findings will also be submitted for presentation at scientific meetings. The study findings will also be presented at relevant national and international conferences.

Patient and public involvement

Patients and public were not involved in the study design, recruitment or conduction of the study. The burden of intervention was assessed by representatives of patient associations participating in the ethical committee. Participants may obtain access to the final results of the study through the local principal investigator.

Discussion

Several recent reviews point out the necessity of high-quality clinical studies in order to improve the level of evidence for the IE management (3–5). The RODEO trials aim to respond to this demand.

Iversen *et al.* in the POET study have recently documented, in a first randomised open-label controlled trial, that a partial oral antibiotic treatment in left-sided IE was non inferior to continued IV treatment and was not associated with unfavourable outcome (16). However, this study had some limitations which could be addressed in the RODEO study. First, strict

inclusion criteria resulted in a large number of exclusions among screened patients (1,554 out of 1,954). We expect that the broader inclusion criteria of the RODEO project will lead to better external validity of the results. Second, unlike the POET study, the oral treatment regimen in our study will be more homogeneous, and closely controlled as the investigational products will be provided and controlled by the trial sponsor. Another limitation in the POET study was the potential bias of merging staphylococci, streptococci, and enterococci for analysis. Indeed, *S. aureus* is regularly isolated as a risk factor for poor outcome in IE (2,19,22), while IE due to streptococci with low minimal inhibitory concentrations (MIC) for amoxicillin could be treated with a short course of IV antibiotic treatment (23).

The RODEO trials will be the biggest multicentre randomised controlled trials to assess non-inferiority of oral switch of antibiotic therapy as compared to entirely intravenous antibiotic therapy in adult patients with left-sided IE due to Gram positive cocci (staphylococci for RODEO 1, streptococci and enterococci for RODEO 2).

If the non-inferiority is confirmed, this strategy could be a way to improve patients' quality of life and reduce IE associated healthcare costs. In order to evaluate this point, a medico-economic evaluation will be conducted alongside the trial.

The pragmatic design of these studies with wide eligibility criteria will permit to evaluate properly the medico-economic analysis, close to the real-life situation.

One of the limitations in the RODEO trials, is that oral regimens are simplified in the experimental arm, contrarily to the recent POET trial which proposed many different oral combinations (16). Several reasons explain that choice. Firstly, the homogeneity of treatment will be easier to interpret in each of the experimental arm. The combination therapy with rifampicin and quinolones has already been approved in other deep infections due to staphylococci (24,25). For streptococcal IE, oral amoxicillin has been recommended with reassuring results (8,13). Then, this is adapted to the French epidemiology of infective

endocarditis with a relative paucity of resistant bacteria (2,22). Therefore, precaution will have to be taken in the extrapolation of the results, notably for IE due to staphylococci resistant to quinolones and enterococci, as MIC are frequently over 0.5 mg/L (26). Then, we choose an evaluation of the primary outcome at 3 months after the end of the treatment as previous studies suggest that most of poor outcomes (mainly death related to IE) occur in the first 3 months after diagnosis (22), and a shorter duration for the evaluation of the primary outcome is supposed to decrease the risk of lost-to-follow-up. The evaluation of a composite score of poor outcome at the end of follow-up is scheduled as a secondary objective. Finally, risk of bias linked with the absence of blinding for the primary outcome measure is attenuated by the use of an independent blinded Endpoint Committee (EC).

The expected non-inferiority of the experimental arm should help to modify the actual recommendations for IE management. Some retrospective studies had already pointed out the interest of oral switch of antibiotic treatment in IE (6,13,15), and a first randomised assay found the same results (16). The RODEO trials will possibly confirm these conclusions and try to demonstrate a potential medico-economic benefit to this strategy.

Their design will also permit to give robust conclusions for both streptococci and staphylococci IE with appropriate power.

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Author contributions

LB conceived and designed the final trial protocol. AC is responsible for the methodological design of the study and designed the protocol for statistical analysis. SBH is responsible for the economic evaluation. AL, LB and AC wrote the first draft of the manuscript. LB, PT, JPB, XD, BH and JLM are members of the scientific committee. AL, LB, PT, JPB, XD, BH, JLM and members of the RODEO study group will be investigators and will recruit patients and conduct the trial. All authors read, reviewed and approved the final manuscript.

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Competing interests None.

Ethics approval Tours Research Ethics Committee (CPP TOURS - Region Centre - Ouest 1, 2015-R26, 23/02/2016).

Data sharing statement

There are no plans to grant public access to the full protocol, participant-level data or statistical code. Data from the RODEO trials is stored by the promotor of the trial. Data and the personal identifiers are stored separately and a special permit is required for access to the data. Data can be available on request for academic researchers when it have been analysed

and published. Qualified researchers can ask for data sharing by the first author LB after the study finalization.

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Table 1: Eligibility criteria for RODEO 1 and RODEO 2 trials

Inclusion criteria
For both trials
Diagnosis of definite left-sided IE according to Duke criteria (3) on native or prosthetic valve
Age ≥18 year old
Appropriate parenteral antibiotic treatment received for at least 10 days
In case of valvular surgery, appropriate parenteral antibiotic treatment received for at least 10 days after surgery
Planned duration of antibiotics of at least 14 days at the time of randomisation (ensuring to have at least 14 days of oral therapy remaining in the experimental group)
Absence of fever (temperature < 38°C) at each time point during the last 48 hours (at least two measures/day) at the time of randomisation
Negative blood cultures for at least 5 days at the time of randomisation
Informed, written consent obtained from patient
Patient covered by or having the rights to French social security
For RODEO 1: left-sided *Staphylococcus* IE
Left-sided IE due to *Staphylococcus* sp. (*S. aureus* or coagulase negative staphylococci) susceptible to levofloxacin and rifampicin
For RODEO 2: left-sided *Streptococcus* IE
Left-sided IE due to *Streptococcus*/*Enterococcus* sp. susceptible to amoxicillin (minimal inhibitory concentrations MIC ≤ 0.5 mg/l)
Non-inclusion criteria
For both trials
Body mass index <15 kg/m² or > 40 kg/m²
Inability or unwillingness to take oral treatment for any reason (digestive intolerance, significant malabsorption) at the time of randomisation
Absence of an entourage to support and watch for him/her at discharge
Expected difficulties regarding compliance with oral antibiotic treatment or follow-up (e.g. severe cognitive impairment, severe psychiatric disease...)
Valvular surgery planned within the next 6 months
Presence of cardiac devices (pace-maker, implantable cardiac defibrillator) with suspected device-related IE without removal of the device
Breast feeding or pregnancy, or women on childbearing age without effective contraception

Expected duration of follow-up < 7 months at the time of randomisation (e.g. expected life expectancy < 7 months, patient living abroad...)
Past medical history of IE in the last 3 months
Other infection requiring parenteral antibiotic therapy after the randomisation
Inclusion in another interventional clinical trial
For RODEO 1: left-sided *Staphylococcus* IE
Glomerular filtration rate < 50 ml/min/1,73m2 for patients with *Staphylococcus* sp (*S. aureus* or coagulase negative staphylococci) infection
Contra-indication to oral antibiotics administered in the experimental arm (i.e. fluoroquinolones or rifampin) - including anticipated non-manageable drug interactions with rifampicin, and allergy or severe intolerance
Taking of an estrogen-progesterone treatment interacting with rifampicin
For RODEO 2: left-sided *Streptococcus* IE
Glomerular filtration rate < 30 ml/min/1.73m2 for patients with *Streptococcus/Enterococcus* sp. infection
Contra-indication to oral antibiotics administered in the experimental arm (i.e. amoxicillin) - including allergy or severe intolerance

Figure 1: Study design

IE: Infective Endocarditis. IV: intra-veinous

Figure 2: Study schedule

*Clinical examination will collect the following information: body temperature, blood pressure, heart murmur (new or modified), any infectious site, list and tolerance of any drug, with a special focus on digestive symptoms, rash, neuropsychiatric complaints.

**Residual concentration of ATB is realized only for patients randomized in “oral therapy” group.

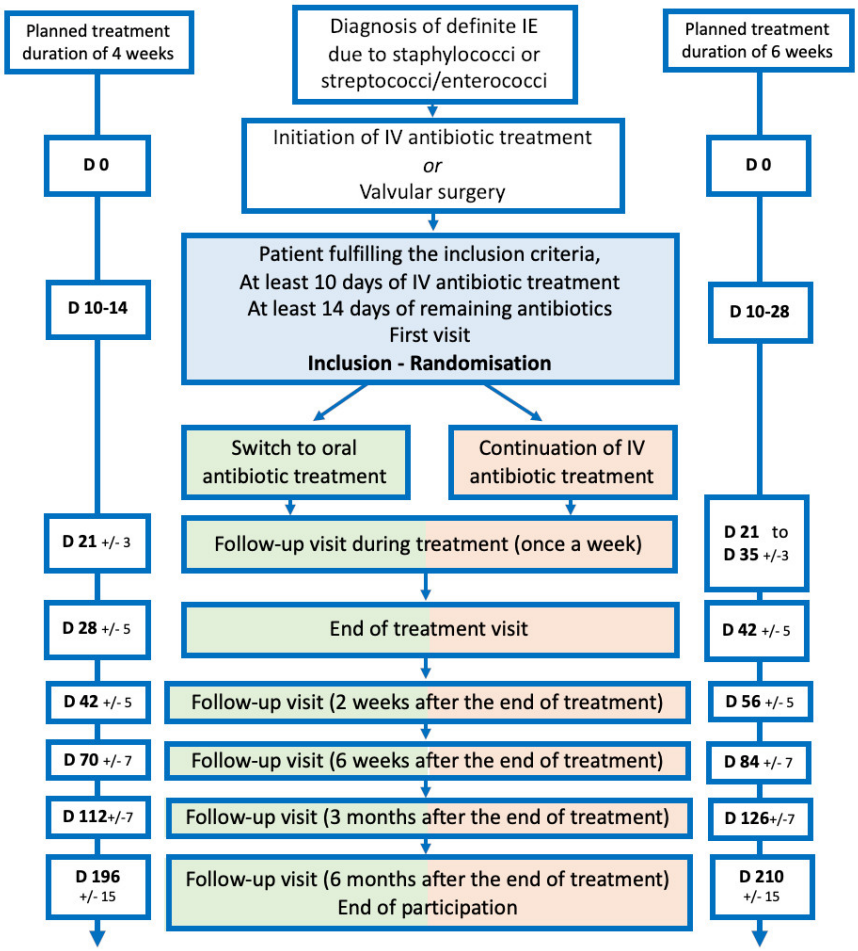

Figure 1: Study design
IE: Infective Endocarditis. IV: intra-veinous

90x90mm (300 x 300 DPI)

	START OF IV ANTIBIOTIC THERAPY/OR VALVULAR SURGERY (D0)	Visit 1	Per treatment visit (once a week thus from 2 to 4 visits according to the remaining treatment duration at randomisation)	After the end of treatment visit (4 visits for each patient i.e 14 days, 1.5, 3 and 6 months after the end of antibiotic treatment)
Patient information		X		
Criteria for inclusion / non-inclusion		X		
Signature of consent		X		
Randomisation		X		
Socio-demographic characteristics		X		
Clinical information				
History of IE		X		
Clinical examination*		X	X	X
Questionnaire				
Quality of life (EQ5D3L)		X	X (at the end of antibiotic treatment)	X (at 3 months and 6 months after the end of antibiotic treatment)
Compliance with antibiotic treatment			X	
Laboratory tests				
Complete Blood Count		X	X	X
C-reactive protein		X	X	X
Liver function tests Albuminemia, glomerular filtration rate		X	X	
Blood cultures (2 bottles, 10 mL/bottle)		X	X	X
Residual concentration of ATB**			X (at visit 2)	
Blood sample for biological collection		X		
Adverse events and concomitant medications			X	X
Echocardiography		X	X (at the end of antibiotic treatment)	X (at 3 months and 6 months after the end of antibiotic treatment)

Figure 2: Study schedule

*Clinical examination will collect the following information: body temperature, blood pressure, heart murmur (new or modified), any infectious site, list and tolerance of any drug, with a special focus on digestive symptoms, rash, neuropsychiatric complaints.

**Residual concentration of ATB is realized only for patients randomized in "oral therapy" group.

106x60mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	19
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-4 & 21
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	2

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11, 13, 18, 21
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8-9
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	9
Objectives	#7	Specific objectives or hypotheses	9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11-12 & 26-27
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-12 & 28-29

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	12-13
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	15
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	26-27
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14-15 & 28-29
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15-16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15 & 17-18
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17-18
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18-19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	19
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results	19

		databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	22
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Available on request
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

BMJ Open

Oral switch versus standard intravenous antibiotic therapy in left-sided endocarditis due to susceptible staphylococci, streptococci or enterococci (RODEO): a protocol for two open-label randomised controlled trials

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Oral switch versus standard intravenous antibiotic therapy in left-sided endocarditis due to susceptible staphylococci, streptococci or enterococci (RODEO): a protocol for two open-label randomised controlled trials

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ABSTRACT

Introduction

Left-sided infective endocarditis (IE) is a serious infection with a heavy burden for patients and healthcare system. Oral switch after initial intravenous antibiotic therapy may reduce costs and improve patients' discomfort without increasing unfavourable outcomes. We describe the methodology of two simultaneously conducted open-label randomised trials aiming to assess non-inferiority of oral switch as compared to entirely intravenous antibiotic therapy for the treatment of left-sided IE.

Methods and analysis

Two simultaneous multicentre open-label prospective randomised trials assessing non inferiority of oral switch during antibiotic treatment as compared to entirely intravenous therapy in patients with left-sided IE are ongoing. One trial is dedicated to left-sided IE caused by multi-susceptible staphylococci (RODEO-1) and the other is dedicated to left-sided IE caused by susceptible streptococci or enterococci (RODEO-2). It is planned to randomise 324 patients in each trial after an initial course of at least 10 days of intravenous antibiotic therapy either to continue intravenous antibiotic therapy or to switch to oral antibiotic therapy. The primary outcome is treatment failure within 3 months after the end of antibiotic treatment, a composite outcome defined by all-cause death and/or symptomatic embolic events and/or unplanned valvular surgery and/or microbiological relapse (with the primary pathogen). Secondary outcomes include patient quality of life, echocardiographic outcome, costs and efficiency associated with IE care. Statistical analysis will be performed with a non-inferiority margin of 10% and a one-sided 2.5% type I error.

Ethics and dissemination:

Written informed consent will be obtained from all participants. This study was approved by Tours Research ethics committee (CPP TOURS-Region Centre-Ouest 1, 2015-R26, 23/02/2016). Study findings will be published in peer-reviewed journals and disseminated through presentation at relevant national and international conferences.

Registration details:

The trials are registered with the European Clinical Trials Database (EudraCT Number: 2015-002371-16) and on clinicaltrials.gov (NCT02701608 and NCT02701595).

Keywords:

Infective endocarditis, oral administration, randomized controlled trial, anti-bacterial agents, adult

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ARTICLE SUMMARY

Strengths and limitations of this study

- RODEO 1-2 trials are multicentre randomised controlled trials appropriately designed and powered to assess non-inferiority of oral switch of antibiotic therapy as compared to entirely intravenous antibiotic therapy in patients with left-sided infective endocarditis
- An economic evaluation, including a cost analysis, a cost-utility analysis and a budget impact analysis, will be conducted alongside the trials.
- In these trials, few regimens are proposed for oral switch, in line with local epidemiology with a relative paucity of resistant bacteria, thus allowing a better homogeneity in the analysis.
- Limitation due to the open-label design of those randomised trials will be limited by the use of a blinded committee to adjudicate the primary outcome. Primary outcome will be measured at 3 months in order to decrease the risk of lost-to-follow-up, the outcome at 6 months being measured as a secondary objective.

Introduction

Infective endocarditis (IE) is a serious infectious disease with a heavy burden for patients and healthcare system (1). In France, median length of hospital stay for patients with IE is 43 days (2) partly linked to the prolonged intravenous (IV) antibiotic therapy recommended by international guidelines (between 4 and 6 weeks in most situations) (3). Current guidelines for IE management are mostly based on expert opinion, *in vitro* studies, animal experiments, or clinical studies performed before the 90's, as very few randomised studies have been conducted (4,5). The only exception to the golden rule of 'IV treatment for all IE' is right-sided IE due to meticillin-susceptible *Staphylococcus aureus* (MSSA), in which the efficacy of an oral combination of ciprofloxacin and rifampicin has been validated in one randomised trial which only included 44 patients (6). Most experts acknowledge that the pharmacodynamic and pharmacokinetic characteristics of antibiotics such as amoxicillin, fluoroquinolones and rifampicin allow a high level of efficacy in the treatment of severe infections due to *S. aureus*, including IE, when orally administrated after an initial phase with adequate IV antibiotic therapy (7–12). A recent systematic review of oral therapy for the treatment of right- or left-sided IE found only one observational study reporting 80% cure rate with oral amoxicillin in 15 cases of streptococcal left-sided IE (13). Two recent studies regarding the management of IE in France showed that a switch from IV to oral antibiotics is feasible when patients with left-sided *Staphylococcus* or *Streptococcus* IE are stable after an initial course of IV antibiotic treatment, with or without valvular surgery (14,15). These practices have not been associated with unfavourable outcome, while significantly reducing the duration and cost of hospitalization, the risk of nosocomial infection, and patients' discomfort. A first randomised trial recently found non-inferiority of partial oral treatment as compared to continued intravenous antibiotic treatment in IE due to Gram-positive cocci whatever its species (16). Other well-designed randomised controlled trials are however

needed to confirm the clinical non-inferiority of this strategy in IE due to most common bacteria (multisusceptible staphylococci, susceptible streptococci or enterococci), specifying for each group of species. Addressing these bacteria in two simultaneously performed trials would ensure an optimal recruitment, reduce cost of research, and argue for/against oral switch in the majority of IE patients. The RODEO project corresponds to two pragmatic open-label randomised trials assessing non inferiority of oral switch during antibiotic treatment as compared to entirely intravenous standard-therapy in patients with left-sided IE. One trial is dedicated to left-sided IE caused by multi-susceptible *Staphylococcus* and the other dedicated to left-sided IE caused by multi-susceptible *Streptococcus* including *Enterococcus*.

Methods and analysis

Study hypothesis

We hypothesise that oral switch for antibiotic therapy is non-inferior to entirely IV antibiotic therapy in the treatment of left-sided IE as assessed by the proportion of patients with treatment failure within 3 months after the end of antibiotic treatment.

Study design

RODEO project comprises two simultaneously performed nationwide, multi-centre, open-label non inferiority randomised controlled trials comparing oral switch with entirely intravenous antibiotic therapy in patients with left-sided IE and an initial course of at least 10 days of effective intravenous antibiotic therapy. One trial is dedicated to left-sided IE caused by multi-susceptible *Staphylococcus* (RODEO-1 trial) and the other dedicated to left-sided IE caused by multi-susceptible *Streptococcus* including *Enterococcus* (RODEO-2 trial). Both trials are based on the same protocol provided below. Nevertheless, they are considered as two distinct trials, and sample sizes were calculated separately so that each trial has 80%

power to show noninferiority of oral switch as compared to standard intravenous antibiotic therapy.

Setting

Trials are ongoing at the time of publication in 28 university hospitals, 14 non university hospitals, 3 private hospitals, and 1 military hospital, all in France. The planned duration of the project is 67 months: 60 months for recruitment, and 7 months for maximal follow-up. The first patient was enrolled on February 29, 2016. End of recruitment is planned on February 28, 2021. At the time of submission, 97 patients have been included in the RODEO 1 trial (staphylococci) and 205 in the RODEO 2 trial (streptococci/enterococci). During the COVID-19 crisis, the maintenance of new inclusions was left to the discretion of the Research Department of the participating centers from March 17 to May 11, 2020. However, the follow-up visits for the patients already included were maintained as planned, in teleconsultation if necessary.

Participants

Eligibility criteria

Patients will be considered for inclusion in a trial if they have a left-sided IE and are in a stable condition after an initial course of at least 10 days of intravenous antibiotic therapy. Full eligibility criteria for both trials are listed in Table 1. Most inclusion or non-inclusion criteria are common to both trials, apart from microbiological diagnosis. Microbiological analyses are not centralised but all participating microbiological wards are certified ISO15-189 and follow the current CASFM/EUCAST guidelines (17). Drug-susceptibility testing follow the EUCAST disk diffusion method (18) and minimal inhibitory concentration (MIC) are determined by broth microdilution or calibrated diffusion strips.

Study recruitment

To better coordinate inclusions, only one department is open in each recruiting centre. All but one are in the Infectious Diseases Unit. Potential participants are identified at the time they are hospitalized and receive IV antibiotic therapy for left-sided IE in one of the participating centres. Patients who meet selection criteria receive a brief study presentation and full participant information sheet by a clinician. After selection criteria confirmation and answering to patient questions about the trial, written informed consent is obtained. Baseline data are collected following consent.

Randomisation

Randomisation takes place between Day 10 and Day 28 after initiation of the IV antibiotic therapy (and at least 10 days of IV conventional antibiotic treatment after valvular surgery, if performed), once the patient fulfils the inclusion criteria without having non-inclusion criteria and at least 15 days of remaining antibiotic therapy. In each trial, participants are randomly assigned in a 1:1 ratio to experimental group (switch to oral antibiotic treatment) or standard treatment (continuation of IV antibiotic treatment). Randomisation is carried out with stratification on whether or not the patient underwent valvular surgery for the control of the current IE episode. There is one random computer-generated sequence for each trial. Centralised randomisation is performed using a secure web-based randomisation system.

Blinding

Patients and care providers are not blinded for pragmatic reasons (oral versus intravenous treatment).

Nevertheless, this potential bias is counterbalanced by the objectivity of primary outcome assessment (described below) and the presence of an independent blinded Endpoint Committee (EC). The EC is composed of one specialist in infectious diseases, one cardiologist and one microbiologist with expertise in IE management, research methodology and experience with clinical trials. The EC will review each suspected case in order to classify

the primary outcome. Adjudication occurs after patients have completed their follow-up. Any disagreements among the EC members will be resolved during conference calls. All decisions made by the Committee are final.

Study interventions

All patients initially receive an IV antibiotic therapy during 10 to 28 days before being randomised if they fulfil the eligibility criteria. The choice of which IV antibiotic agents are used and the expected total duration of antibiotic therapy, from 4 to 6 weeks, should be consistent with the 2015 European Society of Cardiology (ESC) guidelines (3), and is under the responsibility of the physician in charge of the patient. Only patients who still require at least 14 days of treatment for their IE will be randomised.

Experimental group:

Patients switch from initial IV antibiotic therapy to oral antibiotic therapy for the remaining duration of the treatment.

For left-sided IE due to multi-susceptible *Staphylococcus sp.*, patients ≤ 70 kg receive levofloxacin 500 mg once daily in combination with rifampin 600 mg once daily; patients > 70 kg receive levofloxacin 750 mg once a day in combination with rifampin 900 mg once a day, as proposed for prosthetic joint infections (11).

For left-sided IE due to multi-susceptible *Streptococcus sp. o*r *Enterococcus sp* (i.e susceptible to amoxicillin with a MIC ≤ 0.5mg/L), patients ≤ 70 kg receive amoxicillin 1500 mg three times daily and patients > 70 kg receive amoxicillin 2000 mg three times daily.

If an adverse event leads to discontinuation of one antibiotic, the physician in charge of the patient will choose another oral antibiotic agent according to susceptibility testing. The patient will be classified as non-compliant with the strategy if a switch back to IV treatment is needed faced with the impossibility of finishing the remaining oral treatment period.

Control group

Patients continue IV antibiotic therapy for the remaining duration of treatment.

Study outcomes

Primary outcome

The primary efficacy outcome measure is the occurrence of treatment failure within 3 months after the end of the antibiotic treatment. Treatment failure is a composite outcome and is reached once a patient meets at least one of: 1/ Death from any cause; 2/ Symptomatic embolic events defined as secondary osteo-articular, splenic, brain or other symptomatic localization after randomisation. Silent embolic events will not be included; 3/ Unplanned valvular surgery defined as cardiac surgery not planned before randomisation. Surgery due to sterile pericardial effusion or hemorrhage is, however, not included in this end point; 4/ Microbiological relapse (with the primary pathogen) defined as any blood culture positive yielding the same *Staphylococcus sp.* isolate or the same *Streptococcus sp. or Enterococcus sp.* isolate, as the one responsible for the initial episode of endocarditis (i.e. same species, same antibiotic susceptibility profile, the realization of genotypic testing is not mandatory and left to the discretion of investigator).

Failures will be confirmed at the end of the follow-up by an independent endpoint adjudication committee, blinded from group allocation.

We also defined a primary safety outcome of all-cause mortality at day 30 after randomisation which will be analysed after recruitment of one third and two thirds of patients within each trial.

Secondary outcomes

The following variables will be compared between allocation groups as secondary outcomes:

1. As advised for composite outcomes, each component of the primary outcome will also be considered independently.

2. Treatment failure within 6 months after the end of the antibiotic treatment.
3. New infection defined as the recurrence of positive blood cultures with a different pathogen to initial isolate sample within 3 and 6 months after the end of antibiotic therapy.
4. Outcome assessed by echocardiography

Ultrasound examinations will measure: left ventricular ejection fraction, apparition, increase or decrease of the following items: vegetation, abscess, perforation, fistula, dehiscence of a prosthetic valve. A control echocardiography will be performed at the end of antibiotic treatment, at 3 months and 6 months after the end of antibiotic treatment.

5. Catheter related adverse events (AE) and healthcare acquired infections as defined:

- Catheter-related AE: infectious (e.g. catheter-related bacteraemia) or non-infectious catheter-related complications (e.g. extravasation, thrombophlebitis)
- Other healthcare-acquired infections, including urinary tract infections, pneumonia, surgical site infection, *Clostridium difficile* infections

6. Quality of life

We will assess patient's quality of life at the end of antibiotic treatment, at 3 months and 6 months after the end of antibiotic treatment, using the EuroQol Five Dimensions (EQ5D3L)

7. Antibiotic modification

All change regarding antibiotic treatment administered will be recorded (drug, dose or duration). We will assess whether there is a need for a return to IV antibiotic in the experimental (oral switch) group.

8. Compliance with oral antibiotic treatment

The assessment of compliance with oral antibiotic treatment will be carried out at each visit during the treatment period by 2 combined methods: through a "patient leaflet" which will permit to note take/omissions of treatment, filled by the clinician during hospitalization, and

by the patient or his caregivers after returning home; and through the return of the treatments' boxes to the pharmacy of the investigational site, thus allowing a pill count.

9. Economic outcomes

The difference in costs (and length of hospital stays) will be computed from the healthcare system viewpoint between each new strategy of left-sided IE management (depending on the bacteria involved) and the real-life situation. The budget impact of the diffusion of each new strategy will be computed on a three-year timeframe. Incremental cost-utility ratios will be computed to assess the clinical and economic non-inferiority of the two new strategies.

Study procedures

All patients will be followed for a 6-month period following the end of antibiotic treatment. Follow-up is planned as follows: a visit at baseline or Day 1 for randomisation (which is performed between day 10 and day 28 following the start of IV antibiotic therapy), one visit per week during the remaining antibiotic treatment duration, one visit at the end of antibiotic treatment, and one visit at 14 days, 6 weeks, 3 and 6 months following the end of antibiotic treatment (Figure 1 and 2).

Once a subject will be randomized in the study, every reasonable effort will be make to follow the subject for the complete study period even if there is a deviation from the intervention protocols, an early discontinuation of study treatment or if a participant misses one follow-up visit. If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized. All subjects who discontinue study treatment will be encouraged to complete all remaining scheduled visits and procedures.

Data management

Data is recorded on study-specific electronic case report forms (eCRFs) via an electronic data capture system (eCRF model is available on request to the principal investigator). To maintain

participants' anonymity, CRFs are identified only by a patient number and initials. All records that contain patient names or other identifying information will be stored separately from the study records in each centre and can be identified only by the patient number and initials.

Sample size

Sample size calculations are based on a null hypothesis of H0: $\pi 2 - \pi 1 \geq$ delta (ie, inferior); where $\pi 1$ is the proportion of patients expected to experience failure in the intravenous group, $\pi 2$ is the proportion in the oral switch group, and the non-inferiority margin delta is 10%. The alternative hypothesis is $\pi 2 - \pi 1 <$ delta (ie, noninferior).We considered each pathogen separately to ensure that we will have sufficient statistical power to explore non-inferiority of oral switch for staphylococci as well as for streptococci/enterococci. Thus, for each pathogen, *Staphylococcus sp*. and *Streptococcus/Enterococcus sp*., we assumed an expected failure proportion of 10% (3,19,20), taking into account the fact that we will only enrol patients who have a favourable outcome after the first 10 days of IE treatment), a non-inferiority margin of 10%, a one-sided Type I error of 2.5%, and a power of 80%. The number of subjects required is estimated at 145 evaluable subjects per group, thus a total of 290 randomised patients. It is expected that approximately 10% of patients will not be available for the per-protocol outcome assessment, leading to a total of 324 patients to be enrolled, to be sufficiently powered for the per-protocol analysis. The total required sample size is thus 648 patients: 324 patients for the *Staphylococcus sp.* IE (RODEO 1 trial), and 324 further patients with *Streptococcus/Enterococcus sp*. IE (RODEO 2 trial).

Statistical analyses

Statistical analyses will be conducted in both intention to treat (ITT) and per protocol (PP) methodology as recommended for non-inferiority trials. The PP population will exclude patients for whom there is a clear major protocol violation as defined during a blind review prior to any statistical analysis. Analyses will be conducted using two-sided significance tests

at the 5% significance level. A participant flow diagram will be reported. Group characteristics at baseline will be studied with descriptive statistics. No statistical tests will be performed on baseline characteristics. For each trial, the risk of the primary outcome will be estimated within each intervention group. Difference of failure proportions between oral switch (p2) and entire parenteral treatment (p1) for the end of antibiotic treatment will be estimated. We will report point estimate for the between-group difference in failure risks (p2-p1) with its one-sided 97.5% confidence interval calculated using the Wilson score method without continuity correction (21). We will declare oral switch to be non-inferior to parenteral treatment if the upper bound of the one-sided 97.5% CI is less than 10%. This analysis will be performed in both the ITT and PP populations. In the ITT analysis, missing primary outcome data will be handled by assuming that patients with missing data have treatment failure whatever the randomised group (worst case single imputation, assuming data are missing not at random). A sensitivity analysis will be performed excluding patients with missing primary outcome (complete-case analysis, assuming that data are missing completely at random). Another sensitivity analysis with adjustment on the stratification variable (initial valvular surgery for the control of the current IE episode) will be performed using a linear model (identity link function). Subgroup analyses will be performed considering the two strata defined by requirement of valvular surgery before randomisation or not. To assess the impact of a potential centre-effect, a sensitivity analysis of the primary outcome will be performed with a random-centre-effect model. Potential post-hoc sensitivity analyses will be performed. Statistical analysis will be first performed separately for each trial i.e. for staphylococci IE and streptococci-enterococci IE. Then, according to the results, we will consider a pooled analysis.

Concerning secondary objectives, the statistical analysis will be the same as for the primary outcome for the components of the primary outcome. Proportions of abnormalities will be compared using chi-square tests for echocardiographic outcomes.

Healthcare-acquired infection proportions and catheter related non-infectious adverse event proportions will be estimated per group and compared using chi-square tests or Fisher exact tests.

Change in health-related quality of life will be analyzed considering a linear mixed-effects regression model taking into account repeated measures for a given patient.

No imputation of missing data will be performed for the secondary outcomes. Descriptive statistics of compliance with oral therapy will be provided in the experimental group.

Analysis will be performed in SAS 9.4 (SAS institute, Cary NC) and R 3.3 (22) softwares (or latest versions).

Economic evaluation

From the data of three recruiting centres, cost analysis will evaluate, from the healthcare system viewpoint, which strategy between the oral switch (after an IV period of induction) or the IV antibiotic treatment (reference strategy) is less costly.

On this basis, the budget impact on the healthcare system of the diffusion of the oral switch strategy will be computed using a budget impact analysis on a three-years' timeframe.

Direct medical costs will be assessed from the healthcare system perspective in both groups and during the whole induction and follow-up period i.e. 6 months after the end of treatment.

For each patient, we will collect the healthcare resources used both in the hospital setting and primary care services. This covers the initial hospital stay, subsequent hospital stays due to complications/infections, rehabilitation stay, and antibiotics delivered in primary care. Data will be collected from the local hospital discharge databases of three centres (for hospitalizations) and from the CRF of all patients (rehabilitation care and antibiotics).

Using data from all recruiting centres, a cost-utility analysis will be performed to compute an incremental cost-utility ratio "cost per QALY gained". QALY will be computed from the survival data and utility scores obtained from the responses to the questionnaire EQ5D-3L.

Data monitoring

Clinical research associates will ensure that patient inclusion, data collection, registry and rapport are in accordance with the standard operating procedures of the sponsor and the French Good Clinical Practices. They will verify during the quality control visits (at least once a year per centre), in collaboration with investigators: the presence of written consent, compliance with the research protocol, the quality of pre-specified data collected in the case report form and its consistency with the 'source' documents and the management of treatments used.

Moreover, a Data Safety Monitoring Committee (DSMC) comprising two independent clinicians and one independent statistician meets approximately every 6 months to discuss any issues related to patient safety. All serious adverse events will be reviewed by the DSMC as well as interim analysis of the primary safety outcome. Interim analyses of all-cause mortality at 30 days following randomisation will be performed after recruitment of one third and two thirds of patients within each trial. Early stopping rule will be to stop the trial for safety concerns if a P value <0.01 is observed. The role and responsibilities of the DSMC are set out in a written charter. The DSMC provides written recommendations to the trial steering committee following each meeting.

Ethics and dissemination

This protocol was approved by local ethics research committee (CPP TOURS - Region Centre - Ouest 1, 2015-R26, February 23, 2016). An agreement from the French national drug safety agency (ANSM) has also been obtained.

In conformity with the Declaration of Helsinki, all participants sign a written informed consent form that describes this study and provides sufficient information for patients to make an informed decision about their participation. Consent is obtained from patients before they undergo any study procedure. Participants may withdraw from the study at any time during the clinical trial without any impact on their care. In that event, data collected prior to participant withdrawal will be used in the trial analysis. Sponsor of the study may audit trial conduct as deemed appropriate. A formal amendment to the local research ethics committee will be required for any amendments to the study protocol which may impact the conduct of the study, or the potential safety of, or benefits to patients. If needed, an amendment will also be required from the National regulatory Agency for Security of Medicines and healthcare products (ANSM). Any protocol amendments will be communicated to investigators and oversight authority but also to trial participants and registries, if deemed necessary. The 8th amendment was the most recently approved, on December 17, 2018.

Reports will follow international guidelines: CONSORT Statement and Extension of the CONSORT Statement for reporting of non-inferiority and equivalence trials. Research findings will be submitted for publication in peer-reviewed journals regardless of whether or not they are statistically significant. Authors will be individuals who have made key contributions to study design and conduct. Trial findings will also be submitted for presentation at scientific meetings. The study findings will also be presented at relevant national and international conferences.

Patient and public involvement

Patients and public were not involved in the study design, recruitment or conduction of the study. The burden of intervention was assessed by representatives of patient associations participating in the ethical committee. Participants may obtain access to the final results of the study through the local principal investigator.

Discussion

Several recent reviews point out the necessity of high-quality clinical studies in order to improve the level of evidence for the IE management (3–5). The RODEO trials aim to respond to this demand.

Iversen *et al.* in the POET study have recently documented, in a first randomised open-label controlled trial, that a partial oral antibiotic treatment in left-sided IE was non inferior to continued IV treatment and was not associated with unfavourable outcome (16). However, this study had some limitations which could be addressed in the RODEO study. First, strict inclusion criteria resulted in a large number of exclusions among screened patients (1,554 out of 1,954). We expect that the broader inclusion criteria of the RODEO project will lead to better external validity of the results. Second, unlike the POET study, the oral treatment regimen in our study will be more homogeneous, and closely controlled as the investigational products will be provided and controlled by the trial sponsor. Another limitation in the POET study was the potential bias of merging staphylococci, streptococci, and enterococci for analysis. Indeed, *S. aureus* is regularly isolated as a risk factor for poor outcome in IE (2,19,23), while IE due to streptococci with low minimal inhibitory concentrations (MIC) for amoxicillin could be treated with a short course of IV antibiotic treatment (24).

The RODEO trials will be the biggest multicentre randomised controlled trials to assess non-inferiority of oral switch of antibiotic therapy as compared to entirely intravenous antibiotic therapy in adult patients with left-sided IE due to Gram positive cocci (staphylococci for RODEO 1, streptococci and enterococci for RODEO 2).

If the non-inferiority is confirmed, this strategy could be a way to improve patients' quality of life and reduce IE associated healthcare costs. In order to evaluate this point, a medico-economic evaluation will be conducted alongside the trial.

The pragmatic design of these studies with wide eligibility criteria will permit to evaluate properly the medico-economic analysis, close to the real-life situation.

One of the limitations in the RODEO trials, is that oral regimens are simplified in the experimental arm, contrarily to the recent POET trial which proposed many different oral combinations (16). Several reasons explain that choice. Firstly, the homogeneity of treatment will be easier to interpret in each of the experimental arm. The combination therapy with rifampicin and quinolones has already been approved in other deep infections due to staphylococci (25,26). For streptococcal IE, oral amoxicillin has been recommended with reassuring results (8,13). Then, this is adapted to the French epidemiology of infective endocarditis with a relative paucity of resistant bacteria (2,23). Therefore, precaution will have to be taken in the extrapolation of the results, notably for IE due to staphylococci resistant to quinolones and enterococci, as MIC are frequently over 0.5 mg/L (27). Then, we choose an evaluation of the primary outcome at 3 months after the end of the treatment as previous studies suggest that most of poor outcomes (mainly death related to IE) occur in the first 3 months after diagnosis (23), and a shorter duration for the evaluation of the primary outcome is supposed to decrease the risk of lost-to-follow-up. The evaluation of a composite score of poor outcome at the end of follow-up is scheduled as a secondary objective. Finally, risk of bias linked with the absence of blinding for the primary outcome measure is attenuated by the use of an independent blinded Endpoint Committee (EC).

The expected non-inferiority of the experimental arm should help to modify the actual recommendations for IE management. Some retrospective studies had already pointed out the interest of oral switch of antibiotic treatment in IE (6,13,15), and a first randomised assay found the same results (16). The RODEO trials will possibly confirm these conclusions and try to demonstrate a potential medico-economic benefit to this strategy.

Their design will also permit to give robust conclusions for both streptococci and staphylococci IE with appropriate power.

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Author contributions

LB conceived and designed the final trial protocol. AC is responsible for the methodological design of the study and designed the protocol for statistical analysis. SBH is responsible for the economic evaluation. AL, LB and AC wrote the first draft of the manuscript. LB, PT, JPB, XD, BH and JLM are members of the scientific committee. AL, LB, PT, JPB, XD, BH, JLM and members of the RODEO study group will be investigators and will recruit patients and conduct the trial. All authors read, reviewed and approved the final manuscript.

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Competing interests None.

Ethics approval Tours Research Ethics Committee (CPP TOURS - Region Centre - Ouest 1, 2015-R26, 23/02/2016).

Data sharing statement

There are no plans to grant public access to the full protocol, participant-level data or statistical code. Data from the RODEO trials is stored by the promotor of the trial. Data and the personal identifiers are stored separately and a special permit is required for access to the data. Data can be available on request for academic researchers when it have been analysed and published. Qualified researchers can ask for data sharing by the first author LB after the study finalization.

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Table 1: Eligibility criteria for RODEO 1 and RODEO 2 trials

Inclusion criteria
For both trials
Diagnosis of definite left-sided IE according to Duke criteria (3) on native or prosthetic valve
Age ≥18 year old
Appropriate parenteral antibiotic treatment received for at least 10 days
In case of valvular surgery, appropriate parenteral antibiotic treatment received for at least 10 days after surgery
Planned duration of antibiotics of at least 14 days at the time of randomisation (ensuring to have at least 14 days of oral therapy remaining in the experimental group)
Absence of fever (temperature < 38°C) at each time point during the last 48 hours (at least two measures/day) at the time of randomisation
Negative blood cultures for at least 5 days at the time of randomisation
Informed, written consent obtained from patient
Patient covered by or having the rights to French social security
For RODEO 1: left-sided *Staphylococcus* IE
Left-sided IE due to *Staphylococcus* sp. (*S. aureus* or coagulase negative staphylococci) susceptible to levofloxacin and rifampicin
For RODEO 2: left-sided *Streptococcus* IE
Left-sided IE due to *Streptococcus*/*Enterococcus* sp. susceptible to amoxicillin (minimal inhibitory concentrations MIC ≤ 0.5 mg/l)
Non-inclusion criteria
For both trials
Body mass index <15 kg/m² or > 40 kg/m²
Inability or unwillingness to take oral treatment for any reason (digestive intolerance, significant malabsorption) at the time of randomisation
Absence of an entourage to support and watch for him/her at discharge
Expected difficulties regarding compliance with oral antibiotic treatment or follow-up (e.g. severe cognitive impairment, severe psychiatric disease...)
Valvular surgery planned within the next 6 months
Presence of cardiac devices (pace-maker, implantable cardiac defibrillator) with suspected device-related IE without removal of the device
Breast feeding or pregnancy, or women on childbearing age without effective contraception

Expected duration of follow-up < 7 months at the time of randomisation (e.g. expected life expectancy < 7 months, patient living abroad...)
Past medical history of IE in the last 3 months
Other infection requiring parenteral antibiotic therapy after the randomisation
Inclusion in another interventional clinical trial
For RODEO 1: left-sided *Staphylococcus* IE
Glomerular filtration rate < 50 ml/min/1,73m2 for patients with *Staphylococcus* sp (*S. aureus* or coagulase negative staphylococci) infection
Contra-indication to oral antibiotics administered in the experimental arm (i.e. fluoroquinolones or rifampin) - including anticipated non-manageable drug interactions with rifampicin, and allergy or severe intolerance
Taking of an estrogen-progesterone treatment interacting with rifampicin
For RODEO 2: left-sided *Streptococcus* IE
Glomerular filtration rate < 30 ml/min/1.73m2 for patients with *Streptococcus/Enterococcus* sp. infection
Contra-indication to oral antibiotics administered in the experimental arm (i.e. amoxicillin) - including allergy or severe intolerance

Figure 1: Study design

IE: Infective Endocarditis. IV: intra-veinous

Figure 2: Study schedule

*Clinical examination will collect the following information: body temperature, blood pressure, heart murmur (new or modified), any infectious site, list and tolerance of any drug, with a special focus on digestive symptoms, rash, neuropsychiatric complaints.

**Residual concentration of ATB is realized only for patients randomized in “oral therapy” group.

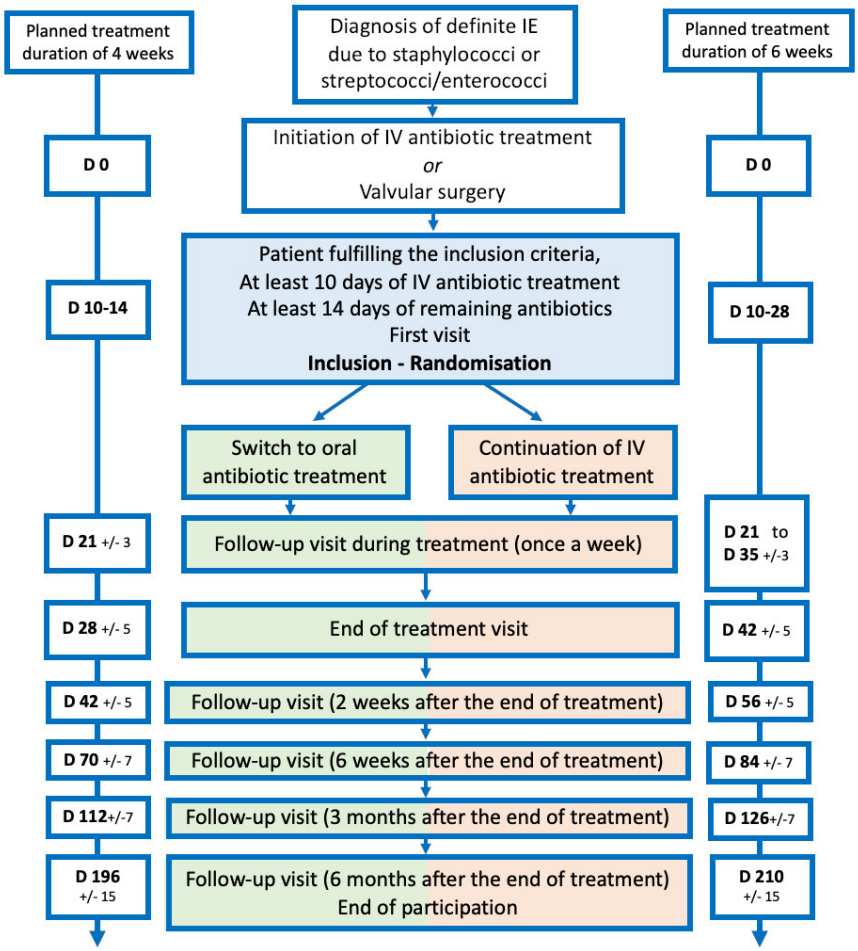

Figure 1: Study design
IE: Infective Endocarditis. IV: intra-veinous

90x90mm (300 x 300 DPI)

	START OF IV ANTIBIOTIC THERAPY/OR VALVULAR SURGERY (D0)	Visit 1	Per treatment visit (once a week thus from 2 to 4 visits according to the remaining treatment duration at randomisation)	After the end of treatment visit (4 visits for each patient i.e 14 days, 1.5, 3 and 6 months after the end of antibiotic treatment)
Patient information		X		
Criteria for inclusion / non-inclusion		X		
Signature of consent		X		
Randomisation		X		
Socio-demographic characteristics		X		
Clinical information				
History of IE		X		
Clinical examination*		X	X	X
Questionnaire				
Quality of life (EQ5D3L)		X	X (at the end of antibiotic treatment)	X (at 3 months and 6 months after the end of antibiotic treatment)
Compliance with antibiotic treatment			X	
Laboratory tests				
Complete Blood Count		X	X	X
C-reactive protein		X	X	X
Liver function tests Albuminemia, glomerular filtration rate		X	X	
Blood cultures (2 bottles, 10 mL/bottle)		X	X	X
Residual concentration of ATB**			X (at visit 2)	
Blood sample for biological collection		X		
Adverse events and concomitant medications			X	X
Echocardiography		X	X (at the end of antibiotic treatment)	X (at 3 months and 6 months after the end of antibiotic treatment)

Figure 2: Study schedule

*Clinical examination will collect the following information: body temperature, blood pressure, heart murmur (new or modified), any infectious site, list and tolerance of any drug, with a special focus on digestive symptoms, rash, neuropsychiatric complaints.

**Residual concentration of ATB is realized only for patients randomized in "oral therapy" group.

106x60mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	19
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-4 & 21
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	2

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11, 13, 18, 21
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8-9
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	9
Objectives	#7	Specific objectives or hypotheses	9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11-12 & 26-27
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-12 & 28-29

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	12-13
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	15
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	26-27
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14-15 & 28-29
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15-16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15 & 17-18
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17-18
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18-19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	19
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results	19

		databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	22
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Available on request
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-